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WITH ABSTRACT OF THE LITERATURE

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On the Effects of Prolonged Exposure to Sulphur Dioxide

Cadmium Poisoning: II. Experimental Cadmium Poisoning

The Reactions of the Organism to Repeated Electric Shocks

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THE JOURNAL OF INDUSTRIAL HYGIENE

VOLUME XIV MAY, 1932 NUMBER 5

ON THE EFFECTS OF PROLONGED EXPOSURE TO SULPHUR DIOXIDE*

ROBERT A. KEHOE, M.D., WILLARD F. MACHLE, M.D., KARL KITZMILLER, M.D., AND T. J. LEBLANC, SC.D.

PURPOSES OF STUDY

IT is highly desirable to have definite information as to whether or not any residual or permanent damage to health is sustained by persons who are employed in trades in which there is continual or frequent exposure to sulphur dioxide. Much of the hearsay information in these trades is to the effect that no injury results from ordinary exposure, and that a marked tolerance is quickly developed. Indeed, it is not uncommon to find workmen who believe their occupational exposure to be beneficial to their health. A body of opinion arising in this way often has some foundation in fact but requires critical investigation before it is accepted.

Furthermore, the common use of sulphur dioxide as a refrigerant, with its consequent introduction into the household, brings about a more than ordinary interest in the effects which may result from its inhalation and absorption. Although it is generally regarded as an irrespirable gas, its presence in the air makes itself known in low concentration and provides a warning which is not likely to be disregarded by an unobserving or even a sleeping person. No accurate information is available, however, as to the limits of concentration borne without immediate or delayed injury, and as to the effects, if any, of prolonged exposure upon life, health, and the incidence of acute or chronic diseased states. It has seemed of some importance, therefore, to make careful studies both under laboratory conditions and under practical conditions of human exposure. The following paragraphs relate to observations of the latter type.

Since the study of sulphur dioxide

* From the Kettering Laboratory of Applied Physiology in the University of Cincinnati, Cincinnati, Ohio.

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was supported by one of the large manufacturers of electric refrigerators,[1] the fullest co-operation in obtaining suitable subjects for observation was assured. A brief survey of the occupations in which exposure to sulphur dioxide is incurred demonstrated that the workrooms of the company's plants presented as nearly ideal conditions for observation as could be found, in that a large number of subjects were available who had had long exposure to a known basic concentration, as well as exposures to high concentrations, which were brief but in many cases frequent. There were also a large number of men of the same type in completely separated departments of the plant, whose ages and general conditions of work and life were similar to those of the subjects under study in every respect save that of sulphur dioxide exposure.

Selection of Subjects

From the workmen who were engaged in handling sulphur dioxide, 100 subjects were selected on the basis of severity and duration of exposure. Among these were forty-seven employees who had had from four to twelve years of exposure. The sulphur dioxide storage and distributing department, the refrigerating unit charging department, and the repair department furnished most of the subjects.

One hundred control subjects were chosen from the assembling departments, tool room, punch press room, carpentry shop, and shipping department, in which there occurred no exposure to sulphur dioxide or to other noxious materials such as paints, lacquers, and metallic dusts. Selection was made on the basis of age groups comparable to those of the exposed subjects.

Severity of Exposure

The charging department of the plant provided a large proportion of the exposed subjects. Here, the units of refrigerating apparatus receive their charge of sulphur dioxide. The liquid sulphur dioxide is delivered to a large number of operating panels through a series of pipes leading from the distributing and storage center. These panels are close together and a large number of operators work in the same room. Thus careless or unskilled breaking of a connection or an accidental leak in a line affects many workmen. In 1927 an effective ventilating system was established in this department, and a system of air analysis was instituted which gave full information as to the concentration of sulphur dioxide present under operating conditions. Figure 1 shows the results of such analyses during the months of August, 1929 and February, 1930. Prior to 1927 the concentration was higher and subject to greater fluctuations, analyses at irregular intervals showing average concentrations of from 80 to 100 parts per million. Under present conditions the concentrations as shown in Figure 1 run somewhat higher during winter months when the windows are closed. During periods of rush production, and when inexperienced operators are being trained, the average concentration is also higher.

The storage and distributing department shows a generally higher concen-

[1] The Frigidaire Corporation of Dayton, Ohio.

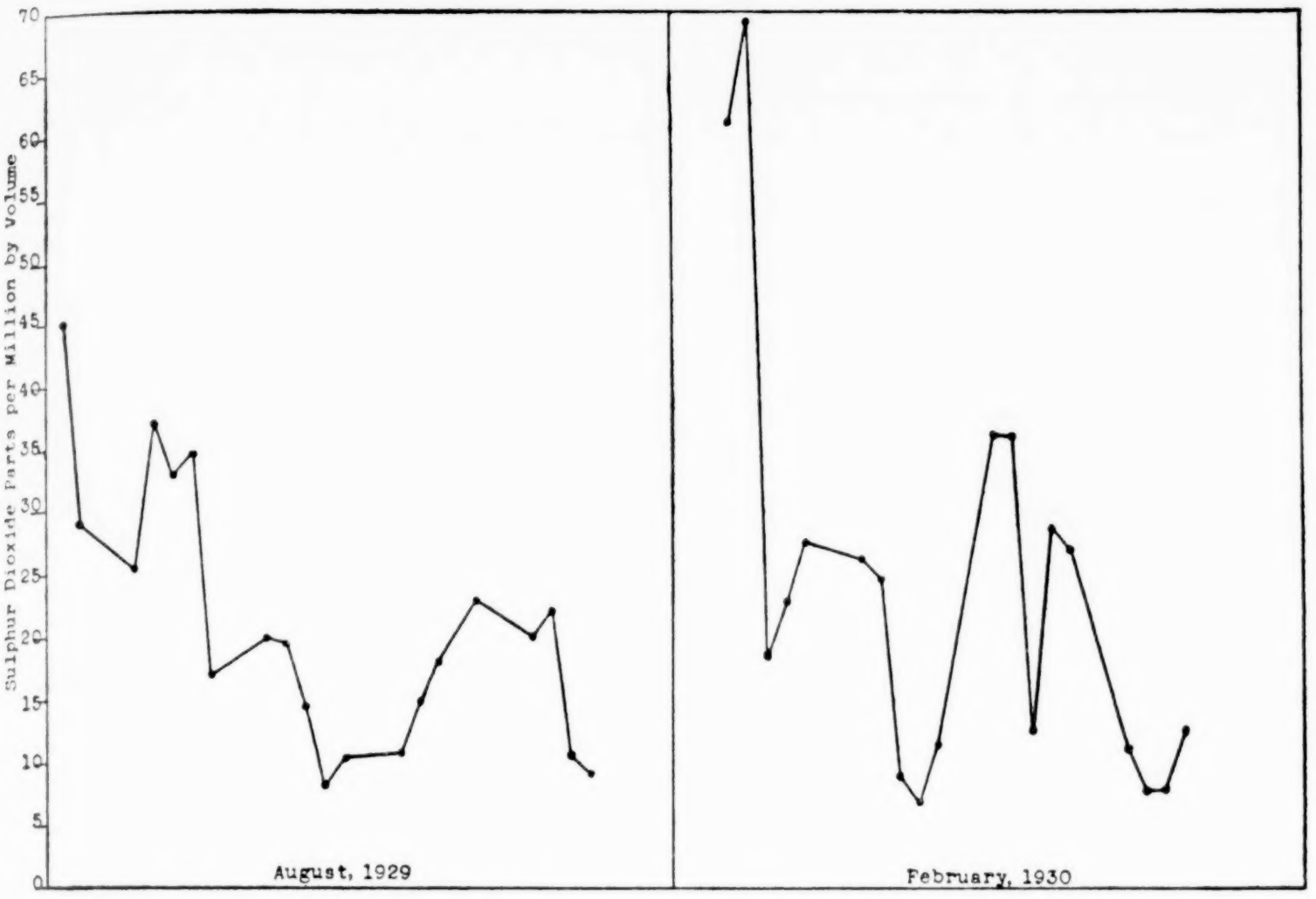

FIG. 1.—Sulphur dioxide content of air in charging room.

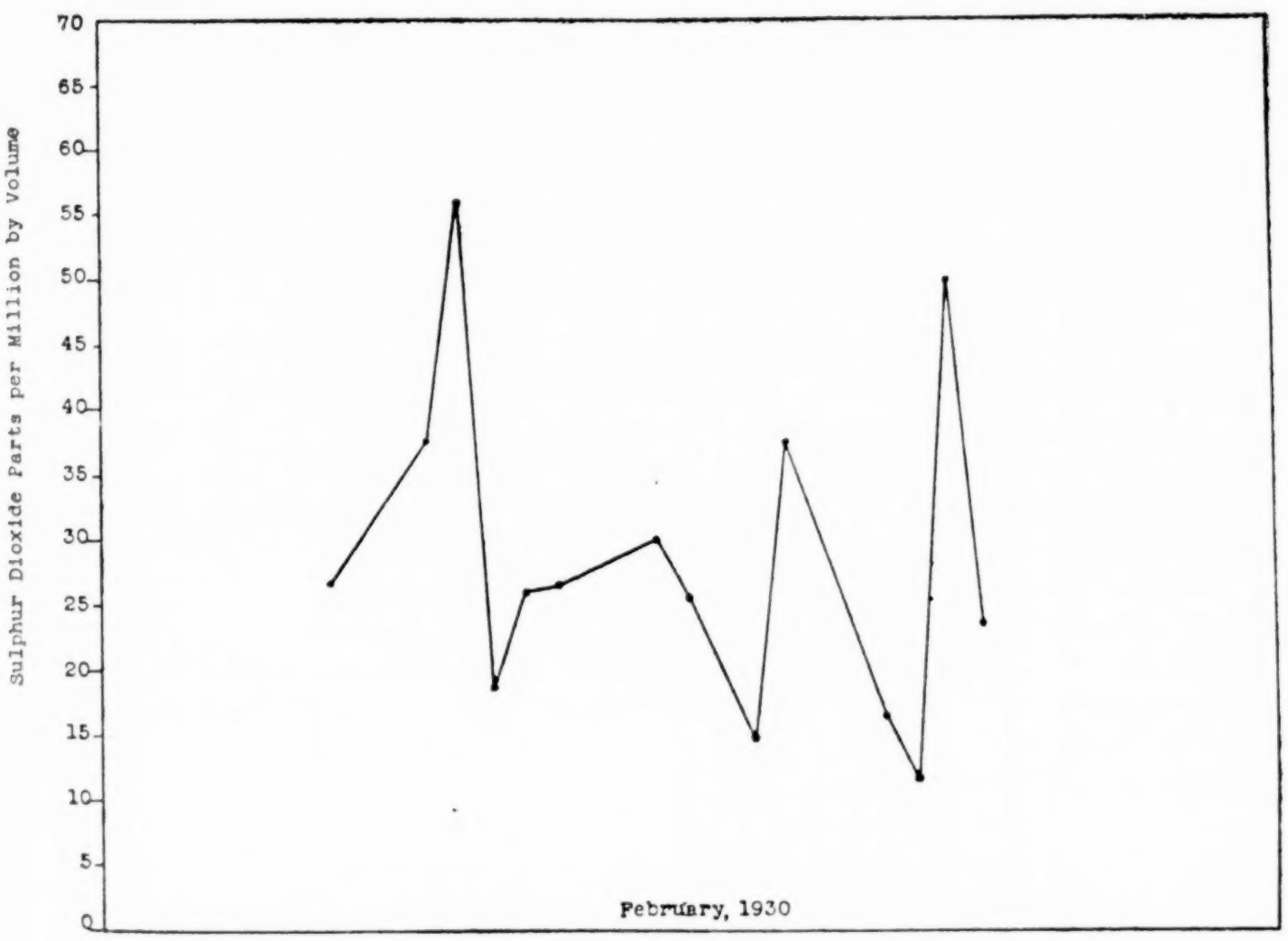

FIG. 2.—Sulphur dioxide content of air in distribution and storage room.

HISTORY SHEET

Number Examiner's Initials Date
Name Age Race Color Birthplace
Marital Ages Children Miscarriages Date Stage
Residence
Other Places Lived in, with Dates
Place of Employment Type of Work (exact description of nature and conditions)
Length of Present Employment and
Previous Employment at Same Work
Previous Occupations Exact Description of Work Done Dates
Gasoline Refining
Lead
Benzene
Lacquer Paints
Paper Manufacturing
Acids
Garage Work
Other Refrigerating Equipment
Previous Illnesses, with Dates:
Tbc. Malaria Rheumatism Lues Gc. Scarlet Diph.
Typhoid Convulsions Heart Disease
Significant Family History:
SO_2 History with Reference to Duration of Exposure, Acclimatization, Injury, Residual Effects, and Recovery:
Sleep Hours in Bed Dreams Restful Disturbed
Consumption per Day { Milk, Cream, Water } { Tea, Coffee, Alcohol }
Bowel Movements Frequency Hour
Tendency to Constipation Cathartics
Tendency to Frequent Stools
Teeth Brushing When Last Trip to Dentist
Usual Weight Best Weight Change of Weight { Seasonal, Occupational }
General Health
Rate of Tiring Recent Change
Headaches Time
Eye Trouble
Taste in Mouth Character Time
Pains in Joints Swelling of Joints
Muscular Strength Cramps in Muscles
Pains in Belly Character Frequency
Appetite Different Meals
Digestive Disturbances Nausea or Vomiting
Skin Infection or Eruption General Hands
Polyuria Nocturia Frequency Pain or Burning on Voiding
Nervousness General Weakness Numbness
Other Complaints
Respiratory History:
Nasal Irritation — Hemoptysis
Frequent Colds — Bronchitis
Cough — Asthma
Sore Throat — Shortness of Breath
Laryngitis

FIGURE 3

J. I. H.
May, 1932

PHYSICAL EXAMINATION SHEET

Number Examiner's Initials Date Height Weight
General Appearance Posture
Nutrition Musculature
Pulse Blood Pressure (seated)
Color of Skin (exact) Sclera
Condition of Skin Glands
Condition of Skin of Hands Tremors
Romberg
Glasses Vision R.15/ L.15/ Near-Sighted Far-Sighted
Eyes: Muscles Pupils Size Regularity
Cornea and Sclera Conjunctiva
Nose Ears: Audition
Abnormalities
Tongue Throat Tonsils
Teeth (exact condition)
Gums (cleanliness) Pyorrhea
Lead Line (exact appearance—location)
Heart: Apex Rate R.C.D. x
After 25 Hops R.S.D.
Two Minutes after
Lungs: K. I.—R. D.E.—R. L.L.B.—R.
L. L. L.
Chest Diagnosis
Abdomen
Liver Spleen Kidneys
Rectum Genitalia
Reflexes {Biceps, Triceps} Abdominal Tendon Jerks Sensations: Painful, Tactile, Thermal, Kinesthetic
Upper Extremities Lower Extremities
Special Remarks and General Diagnosis:

FIGURE 4

LABORATORY SHEET

Number Examiner's Initials Date
Urinalysis: Quantity
Sp. G.
Reaction (Methyl Red)
Albumin (Heller's) Heat and Acetic
Sugar (Fehling's)
Acetone (Nitroprusside)
Microscopic
Blood: White Count Hemoglobin (Dare)
Red Count
Differential (100 cells): Poly. Neutrophils
Poly. Eosinophils
Poly. Basophils
Lymphocytes
Large Mononuclear {Endothelial, Transitional}
Abnormal
Polychromasia
X-Ray Chest Report
Special Examinations:

FIGURE 5

Vol 14
No. 5

tration, averaging approximately 30 parts per million, as shown in Figure 2.

In both the charging and the discharging departments, and especially in the repair department, occasional or frequent escape of sulphur dioxide causes a brief but temporarily unendurable exposure from which the operator finds it necessary to escape.

Methods of Study

Each subject in the two groups was questioned in detail as to the length and nature of his exposure to sulphur dioxide, as well as to other occupational hazards. Care was taken to elicit information as to past and present symptoms and illnesses. The record blanks used as an outline for obtaining information are shown in Figures 3, 4, and 5. No attempt was made to limit the examiner to the subject matter or the details of the blank form, but in each case the findings relating to each item were recorded in a uniform manner.

Under sulphur dioxide history, the examiner recorded all information which could be obtained by inquiring into the following matters:

1. Duration of Exposure
2. Acclimatization
    a. Symptoms of initial period of exposure
    b. Date acclimatization was observed
3. Symptoms Arising from Basic Exposure since Acclimatization
    a. Symptoms from usual minimum amounts
    b. Influence of exposure on common colds (frequency, susceptibility, or prolongation)
4. Heavy (Intolerable) Periodic Exposure
    a. Frequency
    b. Symptoms
        1. Eye, nose, throat
        2. Chest pain and its duration
        3. Aggravation of usual symptoms
        4. Hemoptysis or epistaxis
        5. Hacking cough—night or morning
        6. Polydipsia
        7. Polyuria
        8. Weakness
        9. Appetite and digestion
        10. Headaches and nervous system symptoms
        11. Constipation or diarrhea
5. Residual Symptoms
    a. Altered susceptibility to other chemical or physical irritants
    b. Alteration in sense of taste or smell
    c. Permanent injury of any type

The physical examinations were carefully carried out in a uniform manner, and the laboratory tests of the blood and urine were all made by the same technician. X-ray examinations of the chest of each exposed and each control subject were made by an experienced roentgenologist who also classified the findings in the two groups.

A selected group of subjects representing the severest and longest exposures were studied as to their alveolar carbon dioxide content and their blood plasma carbon dioxide combining capacity. Since the latter tests yielded no information of value, they were not extended to the remainder of the subjects, and they will receive no further mention.

Analysis of Findings

The results of the examinations were subjected to a careful individual and general study, in an attempt to evaluate them properly from a clinical point of view; they were then tabulated and subjected to statistical

analysis by one of the authors (T. J. LeB.). The conclusions arrived at from the study of individual cases are included in those obtained by the application of biometric methods, with the exception of the X-ray findings, to which reference will be made subsequently.

The biometric characteristics of the exposed and control groups are shown in Table 1. Since all the subjects are males, the question of sex is eliminated. The number in each group is the same, *i.e.*, 100. From the table it is seen that the variability as indicated by the respective standard deviations is relatively low and as a result the probable errors of the respective means are low, thus showing that the mean values are stable and that the groups are large enough. The only significant difference exhibited by the table is in the case of years employed in industry, the control group having been employed a significantly longer time than the exposed. In fact, the very close agreement between the respective pairs of means in the case of age, height, weight, and number of years worked in this plant shows that the control group has been exceptionally well chosen and that it constitutes an adequate control for the purpose of this study.

In order to test the validity of the control group further, certain physical findings of a quantitative nature, arrived at by the examination of the clinicians, were analyzed. The resulting constants are listed in Table 2, which in general exhibits the same characteristics as Table 1. Standard deviations are low and the means are stable. Two differences are shown: The polymorphonuclear leukocyte count is *significantly higher in the control group;* the lymphocyte count, on the other hand, is higher in the exposed group. The fact that systolic and pulse pressures, erythrocyte and leukocyte counts, and percentage of hemoglobin as shown by the Dare hemoglobinometer are not significantly different for the two groups constitutes further evidence that the control group is well chosen.

Here it may be noted that in the control group there was a subgroup of twenty-nine individuals who exhibited pallor. The average hemoglobinometer reading for this group was 76 per cent., which was lower than the

TABLE 1.—SHOWING THE MEAN WITH ITS PROBABLE ERROR AND STANDARD DEVIATION FOR CERTAIN VARIABLES

	EXPOSED GROUP		CONTROL GROUP	
	Mean	Standard Deviation	Mean	Standard Deviation
Age in years	37.0 ±0.70	10.40	35.7 ±0.55	8.75
Height in inches	68.1 ±0.21	3.14	68.4 ±0.13	1.96
Weight in pounds	158.5 ±1.87	27.70	153.3 ±1.41	21.00
Years in plant	4.0 ±0.13	1.98	4.5 ±0.17	2.51
Years in industry	8.0 ±0.35	5.26	12.3 ±0.65	9.65

mean of the total of either exposed or control groups.

Physical Findings

All the physical findings on the case records were tabulated, but by inspection a considerable number of them were seen to be of no importance —that is, there was an equal or nearly equal distribution of the findings between the exposed and control groups. This was true of the following rubrics:

Overnutrition, undernutrition, normal pulse, bradycardia, tachycardia, normal temperature, elevated or lowered temperature, adenopathy, tremor, chest findings, cardiac lesions, hypertension and hypotension, abdominal and pelvic lesions, sensory disturbances, skin lesions, impaired vision, lesions of the cornea and sclera, conjunctivitis, chronic nasal discharge, pyorrhea and dental caries.

The remaining findings were not so obvious and were further tabulated. The results are shown in Table 3. It will be noted that the four entries under each pair of rubrics are mutually exclusive and constitute a fourfold table. The Chi-square test applied to the values in this table showed that the differences exhibited were significant. Column 3 lists the values of Chi-square and column 4 shows the value of P arising from the corresponding values of Chi-square, *i.e.*, the probability that the differences shown arose from the operation of chance. In each case this probability is so low that the validity of the difference is almost certainty and the findings have been listed in descending order of *statistical significance*. Emphasis is placed on this point because *clinical significance* may be quite different—that is, a finding might occur with much greater frequency in one group and be of no clinical significance.

TABLE 2.—SHOWING THE MEAN WITH ITS PROBABLE ERROR AND STANDARD DEVIATION, FOR CERTAIN PHYSICAL FINDINGS[1]

PHYSICAL FINDINGS	EXPOSED GROUP		CONTROL GROUP	
	Mean	Standard Deviation	Mean	Standard Deviation
Systolic pressure in mm. Hg	126.7 ±1.30	19.2	124.4 ±1.02	15.0
Pulse pressure	48.5 ±0.78	11.5	48.5 ±0.75	11.1
Erythrocytes	4,784,000 ±29,827	440,000	4,642,000 ±28,517	422,800
Leukocytes	8,170 ±133	1,970	7,840 ±196	2,010
Hemoglobin	80 ±0.59	8.5	81 ±0.45	6.6
Polymorphonuclear leukocytes	61 ±0.56	8.2	*65 ±0.45*	6.7
Lymphocytes	*35 ±0.42*	7.6	32 ±0.48	7.2

[1] Only those entries in italics are statistically significant.

Exposure and Acclimatization

Exposures resolved themselves into a fairly normal frequency which gave the following constants:

Mean length of exposure in years	3.82 ±0.12
Standard deviation	1.81
Modal group in years	2–3.9
Below the modal group	33%
At the modal group	26%
Above the modal group	41%

In addition it may be noted that 74 per cent. of the total exposures fell within the limits of 2 to 4.9 years so that the majority grouped themselves quite closely about the mean, with extremely short and extremely long exposures constituting the remaining 26 per cent. This is also indicated by the standard deviation.

Of this exposed group, 80 per cent. became acclimatized—that is, they acquired the ability to withstand the customary basic exposure without experiencing a notable intensity of the symptoms later described as initial symptoms. The mean length of time necessary for acclimatization was 2.84 ±0.15 months with a standard deviation of 2 months. The standard deviation is high, and is almost equal to the mean. This shows that the variability in time necessary for acclimatization is great, as might have been expected since acclimatization is a personal reaction and as a biologic phenomenon is entitled to relatively high variability. This variability was such that the mode was not defined. Some of this, of course, was due to the fact that acclimatization was not amenable to measurement and the times recorded were reported by each individual, such values necessarily involving not only physiologic variability but variability in intelligence, memory, attention, etc.

TABLE 3.—SIGNIFICANT PHYSICAL FINDINGS[1]

PHYSICAL FINDINGS	EXPOSED GROUP	CONTROL GROUP	CHI-SQUARE	P[2]
Pharyngitis, chronic and slight	70	31	338	0.000000
No pharyngitis	30	69		
Urine acid to methyl red	87	47	41	0.000000
Urine alkaline to methyl red	10	53		
Chronic pharyngitis	38	9	33	0.000000
No pharyngitis	30	69		
Tonsillitis, chronic and slight	34	12	14	0.000180
No tonsillitis	66	88		
Slight pharyngitis	32	22	11	0.000900
No pharyngitis	30	69		
Abnormal reflexes	31	15	7	0.007000
Normal reflexes	69	85		

[1] Arranged in descending order of statistical significance.
[2] P = probability that difference arose through operation of chance.

Symptoms

The symptoms associated with exposure were tabulated in order to determine the frequency of their

occurrence. These came under three headings, as follows: (1) initial symptoms, *i.e.*, developed during the period of exposure before acclimatization; (2) symptoms arising from the minimum or customary exposure with or without acclimatization; (3) symptoms produced by heavy exposure. General symptoms not necessarily associated with exposure, and complaints present at the time of examination were tabulated for comparison of their occurrence in the exposed and control groups.

Initial Symptoms.—The initial symptoms were confined to the respiratory tract. In the descending order of frequency of occurrence they were: irritation of the upper respiratory tract, coughing, epistaxis, constriction in the chest, and hemoptysis. It is of some importance to note that this is almost the exact reverse of the order in which these symptoms would be set on the basis of their clinical significance, as follows: (1) hemoptysis, (2) chest constriction, (3) epistaxis, (4) cough, and (5) irritation of the respiratory tract. When the latter order was used and was set against the frequency of severe exposure, it was found that there was no association between the two. A slight positive association is suggested but this is contradicted by two islands, one showing a relatively high frequency and severity of initial symptoms with low frequency of severe exposure, and the other showing the converse situation. Thus the severity of the initial symptoms is apparently a function of the individual variation of the subjects.

Symptoms Associated with Minimum Exposure.—The symptoms associated with the usual minimum exposure were in the main a much milder form of the initial symptoms. Certain other items appear, however, as expressions of a chronic type of low grade irritation. In the descending order of their frequency these were: hacking cough, morning cough, nasal irritation and discharge, prolongation of common colds, and expectoration. Epistaxis, constricting pain in the chest, and hemoptysis occurred so infrequently as to be of questionable statistical significance. These were classified in the order of their clinical significance, as in the case of initial symptoms, as follows: (1) hemoptysis, (2) pain in the chest, (3) epistaxis, (4) hacking cough, (5) prolongation of colds, (6) morning cough, (7) nasal irritation, and (8) expectoration. These, set against the frequency of severe exposure, did not give the suggestion of an association. Thus with this factor discounted, the severity of these symptoms is seen also to be related to the individual variation of the subjects. It should be said, however, that all the subjects showed some symptomatic evidence of irritation of the upper respiratory tract.

Colds.—The results of the tabulation on colds is summarized as follows:

	Exposed	*Controls*
Total man weeks of colds	1,141	462
Average duration of cold in weeks	13	5.7
No. having no colds for past year	12	19
No. having colds lasting all winter	40	13

The incidence of colds as measured by the number having no colds is not sensibly different in the two groups. The real difference is in the duration

of the cold, which is extended in the exposed group to 2.3 times the average duration in the control group. This fact is also supported by the total man weeks of colds and the number having colds lasting all winter, the values for the exposed group being two to three times those of the control group.

The application of the Chi-square test failed to demonstrate any relationship between the prolongation of colds and the frequency of severe exposure.

Symptoms Associated with Severe Exposure.—The symptoms arising from the irregular exposure to high concentrations were chiefly an intensified form of those occasioned by the original minimum exposure. Coughing and sneezing, conjunctival irritation, and soreness of the throat and larynx were the most frequent results of such exposure, while thirst, weakness, transitory chest pains, loss of appetite for the succeeding meal, polyuria, and chest pain of a more or less prolonged type were sufficiently frequent to be taken into account. These facts merely demonstrate the incompleteness of the acclimatization.

General Symptomatology

A comparison of the general symptomatology of the two groups showed that many of the symptoms had no relationship to sulphur dioxide exposure. That is to say, they occurred with approximately equivalent or lower frequency in the exposed as compared with the unexposed group. This situation existed in the case of the following:

Skin eruptions during employment, weight gain in employment, weight loss in employment, poor general health, bad taste in mouth, joint pains, abdominal cramps, loss of appetite, dyspepsia or vaguely described digestive disturbances, constipation, diarrhea, nocturia, burning on urination, headache, disturbed sleep, nervousness, numbness or tingling of extremities, general weakness, frequency of colds, sore throat or laryngitis, bronchitis, asthmatic attacks, and eye troubles. (See Table 4 for comparative frequencies of certain items.)

A significant increase was found, however, in the frequency of occurrence in the exposed subjects of shortness of breath on exertion, increased fatigability during employment, altered sense of taste or smell, and increased sensitivity to other irritants. Table 5 shows the application of the Chi-square test to these items.

Only two of these complaints occurred with sufficient regularity in the exposed group to be subjected to further analysis, *i.e.*, an increased fatigability during employment and shortness of breath on exertion. The relationship of these to the frequency of severe exposure was studied by arranging fourfold tables as shown in Table 6. The average number of severe exposures per man per annum was 230. This was used, therefore, as the dividing line between high and low frequencies of severe exposure. The Chi-square test under these conditions showed that the occurrence of each symptom was positively correlated with the frequency of severe exposure.

X-Ray Findings

Each group of subjects (exposed and control) was classified by the roentgenologist into four subgroups made up according to the results of the chest examinations: (1) average

TABLE 4.—FREQUENCY OF CERTAIN SYMPTOMS HAVING NO STATISTICAL SIGNIFICANCE

SYMPTOMS	EXPOSED GROUP	CONTROL GROUP
Weight gained	17	13
No weight gained	61	77
Weight lost	22	10
No weight lost	61	77
Alteration in health	5	2
No alteration in health	95	98
Tendency to constipation	33	42
No tendency to constipation	67	58
Complaint of headaches	16	12
No complaint of headaches	84	88
Headache and constipation	9	9
Headache and no constipation	7	3
Constipation and headache	9	9
Constipation without headache	24	33

TABLE 5.—FREQUENCY OF CERTAIN SYMPTOMS OF STATISTICAL SIGNIFICANCE[1]

SYMPTOMS	EXPOSED GROUP	CONTROL GROUP	CHI-SQUARE	P
Alteration in sense of smell	14	0	15	0.0001
No alteration in sense of smell	86	100		
Increase in sensitivity to other irritants	14	0	15	0.0001
No increase in sensitivity to other irritants	86	100		
Shortness of breath on exertion	42	19	12	0.0005
No shortness of breath on exertion	58	81		
Increase in fatigability in employment	27	9	11	0.0009
No increase in fatigability in employment	73	91		
Alteration in sense of taste	10	0	11	0.0009
No alteration in sense of taste	90	100		

[1] Arranged in descending order of statistical significance.

normal chests; (2) chests in which there may be slight reasons for suspecting the existence of pathologic development; (3) chests in which the

existence of disease, active or healed, is suspected; (4) chests in which there is definite lung pathology. In accordance with this classification the two groups are compared in Table 7.

There was nothing peculiar in the appearance of the roentgenograms of the exposed subjects, and nothing from an X-ray point of view to indicate the existence of injury to the lungs or bronchi as a result of the exposure. The four cases showing chest pathology in the exposed group consisted of three in which an abnormal amount of peribronchial infiltration with mottled areas in the lung tissue suggested the existence of active infection, and one in which thickening of the pleura and calcified areas in the lung tissue indicated the presence of either a chronic or a healed disease process. Upon checking these findings with the histories of previous illness and the physical findings, one case was seen to be a chronic bronchitis of long standing, two were instances of chronic nasopharyngitis with a degree of involvement of the respiratory passages characteristic of this condition, while the last-mentioned was a case of healed pleuritis, the acute illness having occurred over a period of four months in 1901.

The four cases in the control group were made up of three cases of peribronchial infiltration, with areas of calcification in the lung tissue, the former finding being associated with

TABLE 6.—RELATIONSHIP OF CERTAIN SYMPTOMS TO FREQUENCY OF SEVERE EXPOSURE

SYMPTOMS	EXPOSURES PER ANNUM		CHI-SQUARE	P
	Below 230	Above 230		
Shortness of breath on exertion	24	18	7	0.0082
No shortness of breath on exertion	49	9		
Increase in fatigability in employment	14	13	8	0.0047
No increase in fatigability in employment	59	14		

TABLE 7.—FINDINGS BY X-RAY EXAMINATION OF CHEST

GROUP	CLASSIFICATION	NO. OF SUBJECTS	
		Exposed to SO_2	Not Exposed to SO_2
1	Average normal chests	70	64
2	Slightly suspicious chests	14	12
3	Suspicious chests	7	9
4	Definite chest pathology	4	4
Total no. of persons observed		95	89

chronic rhinitis, and one case of healed, infected gunshot wounds of the chest.

Discussion

The interpretation of the main results of the foregoing analysis is essentially self-evident. Exposure to sulphur dioxide under the conditions observed produces two distinct sets of effects: (1) irritation of the upper respiratory tract, which is at first acute in character, and subsequently subacute or chronic; and (2) systemic symptoms of a mild type such as are associated with any type of increased acid absorption or production in the tissues. The high degree of correlation shown between the systemic symptoms and the frequency of severe exposures indicates that the human organism has a high degree of adaptability to a regular moderate exposure, and that it suffers no apparent injury from such an exposure. In the case of intense exposures, even though they occur frequently, there is no evidence of damage of a serious or a permanent type.

It might be expected that the effects of a persistent chronic rhinitis and pharyngitis would be more noticeable in the production of systemic symptoms and in the development of chronic disease of the lungs and bronchi. The absence of such results leads one to suspect that the irritation of the upper respiratory tract is not regularly associated with infectious processes. If this should be found to be true it would follow that the persistent "colds" described by many of the subjects are not colds in the ordinary sense, but rather a chronic coryza due to chemical irritation.

The variation in the relative numbers of the types of leukocytes in the two groups is not so readily interpreted. Lymphocytes occur with higher than normal frequency in both groups. This not uncommon finding is probably associated with the high incidence of low grade chronic infection of the nose, mouth, and throat in both groups. The difference in the two groups, while of statistical significance, is of doubtful clinical importance. A much greater difference would be required to establish any certainty in this regard.

The matter of abnormal reflexes requires some further consideration. Under this heading were listed sluggish and hyperactive reactions. In no case were the abnormalities of the type associated with localized lesions of the central nervous system. They signify, therefore, a degree of variation in general irritability. It would be presumptuous to ascribe any important clinical significance to such variation.

The roentgenograms show that no appreciable residual injury to the lungs and bronchi has been produced by the exposure to sulphur dioxide, either of a prolonged or of a severe type. It cannot be doubted that injury to the pulmonary epithelium occurs when high concentrations are inhaled. Nor can one doubt the significance of hemoptysis, constricting pain in the chest, and a deep productive cough after a period of intense exposure. It is clear, however, that under the conditions of exposure here considered, no permanent damage is done to the lungs.

Considering the number of subjects studied, the variety of their exposure, and the number who did not become acclimatized to exposure but who never-

theless continued to be exposed, it would seem reasonably certain that the foregoing observations represent an adequate cross-sectional picture of the results of exposure to sulphur dioxide. On this basis it may be concluded that there is no appreciable danger to health in a frequent or more or less continuous exposure to endurable concentrations, and that the effects of exposure to unendurable concentrations are negligible under conditions which allow of quick escape.

Summary

1. A significantly higher incidence of nasopharyngitis, both chronic and slight, of alteration in sense of smell and sense of taste, and of increased sensitivity to other irritants was found in a group of workers exposed to sulphur dioxide. These may be thought of as conditions arising from local irritation.

2. A significantly higher incidence of abnormal urinary acidity, of tendency to increased fatigue, of shortness of breath on exertion, and of abnormal reflexes was found in the exposed group. These are in the nature of systemic symptoms.

3. There was no demonstrable association between frequency or severity of initial symptoms and frequency of heavy exposure, nor was there any relation between exposure and the frequency and severity of symptoms arising from the customary exposure.

4. A positive relation exists between frequency of heavy exposure and presence of certain symptoms indicative of acid accumulation, namely, increased fatigability during the period of employment, and shortness of breath on exertion.

5. The incidence of colds is not significantly different in the two groups. The duration, however, is extended in the exposed group.

6. In all other respects as indicated in the text, there was no significant difference between the two groups.

CADMIUM POISONING: II. EXPERIMENTAL CADMIUM POISONING*

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GENERAL CONSIDERATIONS

POISONOUS substances may enter the body through the respiratory system, the gastro-intestinal tract, the mucous surfaces (conjunctivae, nasal mucosa, and buccal mucosa), and the skin (broken or unbroken). The reactions and changes produced are dependent on many factors, the most important of which are the manner of entrance into and excretion from the organism, and the concentration, duration (time of exposure), and physicochemical properties of the poison. The physicochemical properties are especially important and sometimes enable us to foresee the possible changes which may occur in the organism as a result of their action.

Cadmium is classed as a heavy metal and consequently should have the same properties as the heavy metals. Briefly, according to Flury and Zangger (1), the heavy metals have the following pharmacologic characteristics: great atomic weight and consequently great specific gravity or density; a tendency when in contact with organic material to form complex metal albumin compounds; a general toxic action which may lead to inflammation and degeneration of different organs, and frequently cause injury to the capillaries. The soluble metal albumin compounds are more noxious because they have a more profound action, and because they are resorbed more rapidly. As a secondary noxious action we have the elaboration of acids at the moment of formation of metal albumin compounds.

In the consideration of cadmium as an industrial health hazard, we have to deal with a poison which enters the body mainly through the respiratory system, and secondly through the gastro-intestinal tract. Consequently observations on poisoning through the respiratory system are of greater value. In studying any kind of poisoning we are interested not only in the acute and chronic action of the poison, and the sequelae, but also in the fate of the poison after its entrance into the body—resorption, distribution, and elimination. The most common kind of cadmium poisoning is the acute respiratory form resulting from exposure in manufacturing and handling cadmium compounds. Serious acute poisoning through the gastro-intestinal tract is improbable for man

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owing to the emetic effect of cadmium; and since cadmium is not absorbed through the unbroken skin, poisoning cannot occur in this manner.

The observations here reported were made on cats poisoned with cadmium oxide fume, cadmium oxide dust, and cadmium sulphide dust. These compounds were chosen because of their frequent use. Cadmium sulphide was especially included because it is believed in some industries to be harmless. In general the experimental animals were killed by bleeding, and after specimens were taken for microscopic study the organs were analyzed for cadmium. The method of cadmium analysis described by Fairhall and Prodan (2) was employed in all the chemical work and proved uniformly satisfactory.

Poisoning by Inhalation

Cadmium Oxide Fume

High Concentrations:

Two cats (Cats 1 and 2), subjected to very highly concentrated fume, were exposed separately for thirty minutes in a wooden box of about 150 liters' capacity. The fume was generated in a pyrex glass tube connected to the box at one end and to an oxygen tank at the other. Small pieces of metallic cadmium were placed in a bulb blown at the middle of the tube; this was heated from below by a Bunsen burner and a gentle stream of oxygen was blown through. The molten cadmium was then ignited by means of a glowing splint and the combustion of the metal proceeded evenly, with the abundant production of cadmium oxide fume. Cat 1 was killed by bleeding five hours after exposure; Cat 2 died about twelve hours after exposure.

Symptoms.—About ten minutes after exposure was started the cats showed an abundant salivation, rather thick in character, and an increased respiration (panting). After they were taken out of the box the salivation continued and they showed great difficulty in respiration, stretching out their forefeet so that the accessory respiratory muscles entered into action.

Autopsy.—The lungs showed congestion with several emphysematous patches at the bases, and were more solid than normally. The mediastinum was edematous, and Cat 1 showed a yellowish pleural effusion. On section the lungs exuded a pink-colored, aerated liquid. The trachea appeared normal; a few of the bronchioles were filled with froth. The liver in both cats had a fatty appearance. The rest of the organs were very congested.

Microscopic Findings.—The lungs (see Fig. 1) of both cats showed extensive acute injury, with the following outstanding changes: edema, injury to the bronchioles and alveolar ducts manifested by desquamation of the epithelium, polymorphonuclear leukocyte infiltration in the walls, and edema of the walls. Acute alveolar emphysema was present and a small amount of fibrin was found in the alveolar spaces.

The liver presented different lesions in the two cats. Cat 1 showed slightly swollen cells with prominent marginal borders, and uniformly vacuolated and granular cytoplasm. Cat 2 showed extensive fatty infiltration (about half of the total liver cells were filled with fat), and polymor-

phonuclear leukocyte infiltration in some areas.

The kidneys in Cat 1 showed marked fatty degeneration, mostly in the convoluted tubules, and badly swollen

Chemical analysis of the organs of Cat 1 showed that the cadmium content was highest in the lungs, next in the liver, and third in the kidneys (see Table 1 and Fig. 2).

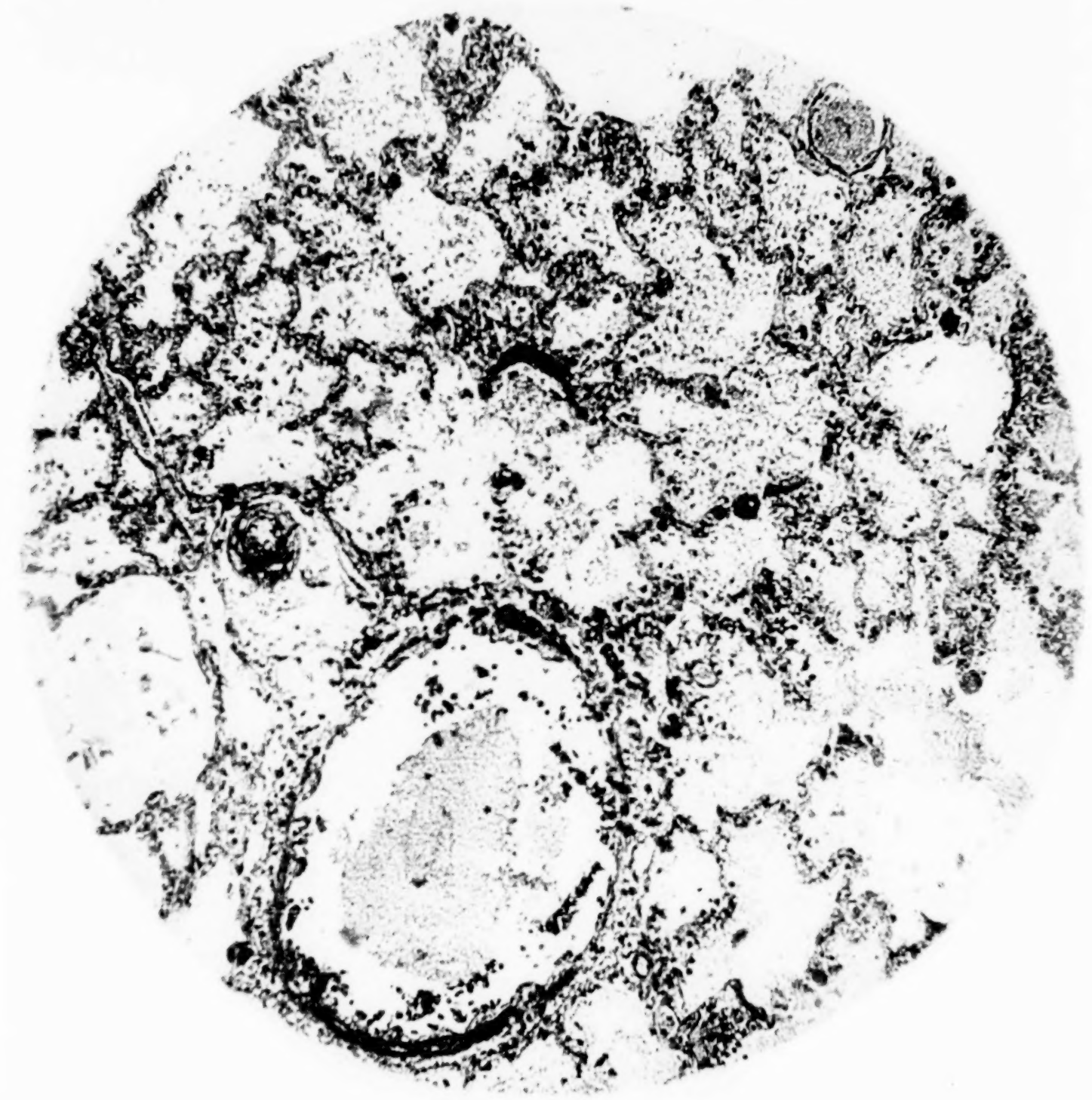

FIG. 1.—Lesions occurring in lungs of cats poisoned with high concentrations of cadmium oxide fume. Showing extensive edema and emphysema, and epithelial desquamation and fibrin precipitate in alveoli and bronchioles. × 300.

cells. Some fat in the form of medium-sized vacuoles, chiefly in the convoluted tubules, was found in Cat 2. The other organs presented no pathologic changes.

Low Concentrations:

After it was observed that high concentrations of cadmium oxide fume were fatal, Cats 3, 4, and 5 were exposed in a gas chamber to less

concentrated cadmium oxide fume for twenty-four hours. Samples of the air in the chamber were taken from time to time in order to determine the exact concentration of cadmium during the experiment. A typical concentration curve (or settling curve) is given in Figure 3. The first sample was

TABLE 1.—CADMIUM CONTENT OF TISSUES OF CAT 1, POISONED WITH HIGHLY CONCENTRATED CADMIUM OXIDE FUME

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM IN 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	127.0	traces	.....	.....
Lungs	69.0	2.50	3.62	46.30
Liver	112.0	1.90	1.70	35.20
Kidneys	54.0	0.60	1.11	11.10
Bile	1.8	0.25	13.90	4.62
Urine	2.5	0.15	6.00	2.78
Total	.....	5.40	.....	100.00

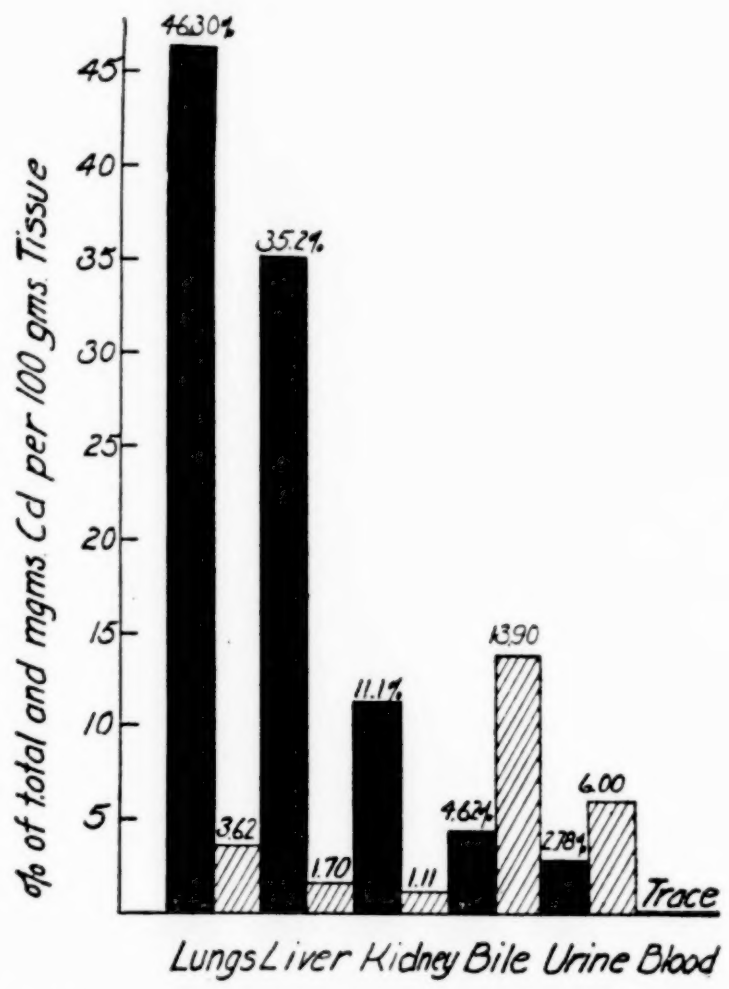

FIG. 2.—Distribution and concentrations of cadmium in tissues of Cat 1.

Solid black columns represent percentages of total cadmium found by analysis in different organs. Cross-hatched columns represent milligrams of cadmium per 100 gm. of fresh tissue.

taken two hours after setting up the fume; the initial concentration was therefore estimated from this concentration curve and was found to be 18 mg. per cubic meter of air. The fume was generated in the same manner as for Cats 1 and 2, by burning cadmium in a pyrex glass tube with oxygen.

Symptoms.—After about twelve hours of exposure the cats began to salivate and showed an increased rate of respiration. They refused to eat or drink and became very depressed. At the end of the exposure all three cats were salivating and showed difficulty in breathing. Cat 3, which had the symptoms in most accentuated form, was killed by bleeding. The blood count before exposure was 7,432,000 for red cells, and 16,500 for white cells; after exposure it was 8,824,000 for red cells, and 29,600 for white cells.

Cats 4 and 5 appeared very sick on the days following exposure. Their respiration was difficult and they refused to eat. Cat 4 was killed by bleeding on the fifth day after exposure, and Cat 5 on the ninth day.

Autopsy.—In Cat 3 the lungs appeared very congested and of dark reddish-brown color, more solid than usual and with emphysematous patches. On section a very little aerated, reddish-brown liquid escaped from them. The trachea was slightly reddened. The liver had a fatty appearance. The rest of the organs were normal, except for congestion.

Cat 4 showed changes very similar to those observed in Cat 3. The lungs in Cat 5 were extremely congested and of very dark-brown color, with emphysematous patches. On section, after the blood content had been expressed, they did not collapse.

Microscopic Findings.—Cat 3 showed a moderate thickening of the alveolar walls in the lungs as the most striking change, with interstitial and perivascular edema and early poly-

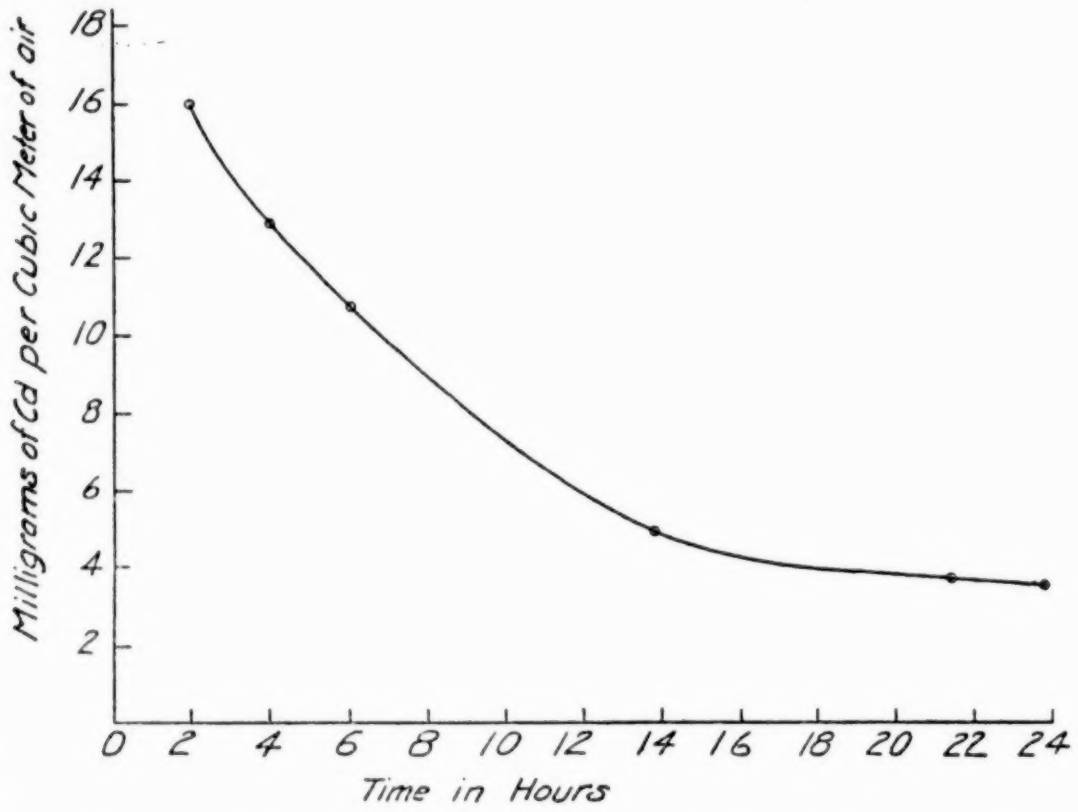

FIG. 3.—Typical settling curve of cadmium oxide fume.

morphonuclear leukocyte infiltration. Other findings included extensive hemorrhage; atelectatic regions and acute emphysema; desquamation of the epithelium and hemorrhage in the bronchioles; and polymorphonu-

TABLE 2.—CADMIUM CONTENT OF TISSUES OF CAT 4, POISONED WITH LESS CONCENTRATED CADMIUM OXIDE FUME

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM IN 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	36.0	traces	.....	.....
Lungs	27.5	0.39	1.42	21.67
Liver	57.0	0.35	0.61	19.44
Kidneys	12.6	0.20	1.59	11.11
Bile	2.5	0.12	5.00	6.67
Urine	1.0	0.10	10.00	5.56
Heart	10.0	0.15	1.50	8.33
Spleen	3.5	0.07	2.14	3.89
Pancreas	3.5	0.07	2.14	3.89
Feces	10.5	0.35	6.67	19.44
Total	....	1.80	.....	100.00

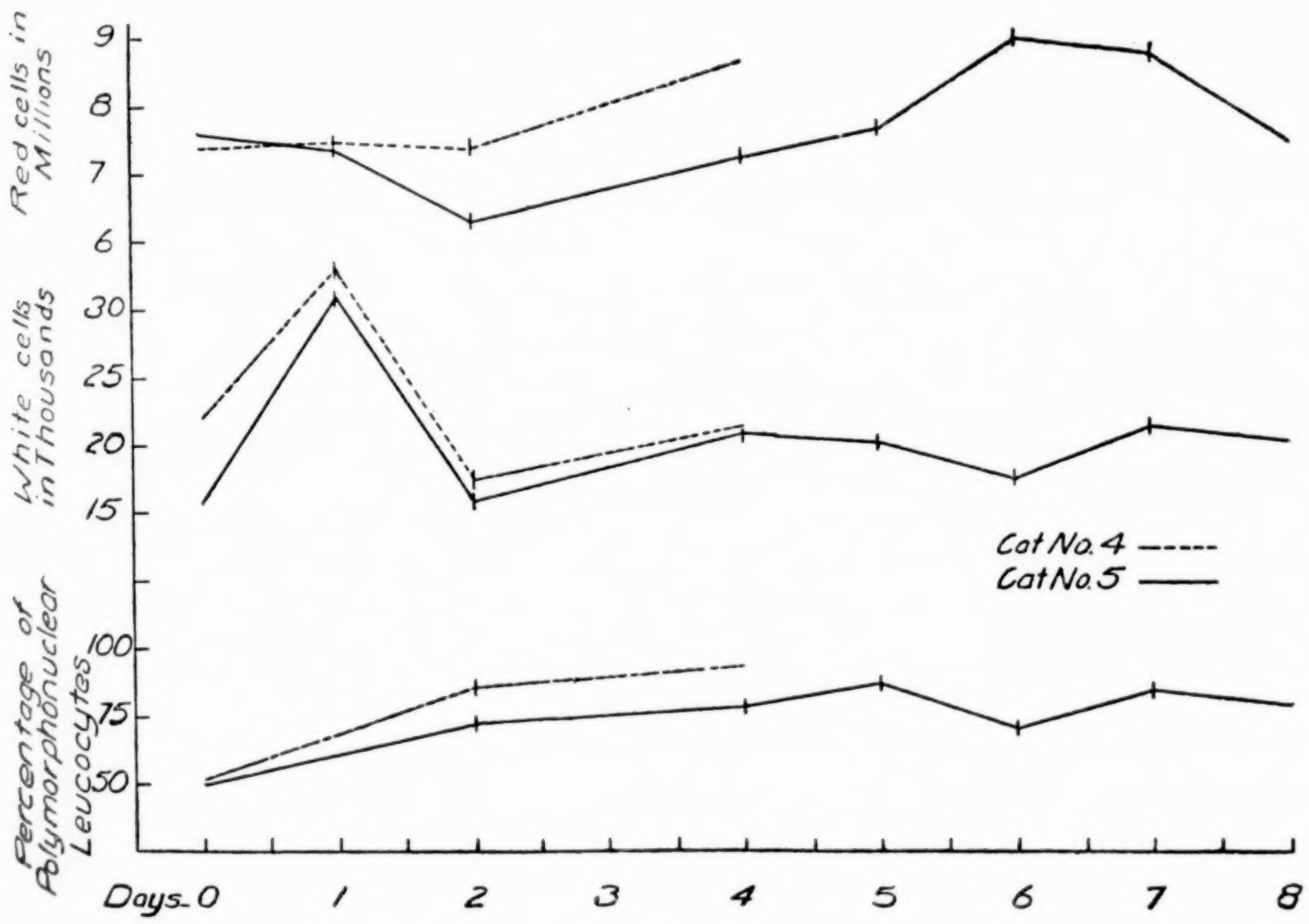

FIG. 4.—Blood variations of Cats 4 and 5. (The first sample was taken before exposure.)

clear leukocytes in the walls of the bronchioles.

The liver showed numerous granular vacuolated cells, especially around the central vein, and here and there the nucleus was destroyed. The architecture was not disturbed and the sinusoids were empty. The cells were slightly swollen and the epithelial border was prominent. The kidneys showed a moderate amount of fat in the tubular epithelium.

The changes in Cat 4 were very similar to those in Cat 3. The most prominent change in the lungs of Cat 5 was the marked thickening of the alveolar walls, which showed extensive hemorrhage, marked fibroblastic proliferation, and a moderate degree of inflammatory cell infiltration. The liver and kidneys showed changes similar to those found in Cats 3 and 4. The other organs were negative.

The chemical analysis of the tissues of Cat 4 is presented in Table 2.

Blood Changes.—The blood changes in Cats 4 and 5 are shown in Figure 4. There we see a tendency toward increase in the red cells; the white cell count increases abruptly on the day immediately following exposure, but drops back on the third day, and subsequently fluctuates around the normal point. The polymorphonuclear leukocytes, however, maintain a definite tendency to increase—in Cat 4 from 51 per cent. to 94 per cent. in four days, and in Cat 5 from 50 per cent. to 80 per cent. in eight days, with slight fluctuations during this period. The microscopic study of the blood smears showed more or less normal appearance with no abnormal cells except in Cat 4 which showed one normoblast in a whole slide on each of the last two days before it was killed.

Discussion:

The problem of how much cadmium was inhaled by the cats and how much was retained in the lungs is most important. Although these questions cannot be answered with accuracy, they may be answered approximately. Saito (3), in his experiments on dogs and on one rabbit, obtained from 4 to 24 per cent. dust (white lead) retention in the lungs. Cecil K. Drinker and his coworkers (4) observed that the natural protection of the lungs of cats, rabbits, and rats against the inhalation of dust was very great and was influenced by different factors, such as quiescence and light breathing. Philip Drinker and his coworkers (5), in a study of the retention of dust and fume by man, found that for zinc oxide powder it averaged 56 per cent. and for zinc oxide fume 57 per cent. Brown (6) points out different factors that influence the dust retention—inspired dust concentration, particulate size, density, wettability, and rate of respiration. He concluded that with a respiration rate over 20 per minute the dust retention is effected only by impingement and is about 40 per cent. for man.

Normal cats breathe about seventy times per minute. In the present research, after about twelve hours of exposure the breathing of the cats increased to approximately 100 times per minute, an unfavorable condition for the retention of fume or dust. The volume of air inspired is known to be about 300 c.c. per minute per kilo of cat. From these figures and from

the concentration curve (Fig. 3) it was possible to calculate the theoretical cadmium content in the inspired air. The percentage retention was calculated from the results of the chemical analysis.

From Table 3 it may be concluded that the cats had inhaled from 6 to 12 mg. of cadmium—the maximum possible amount under the conditions of the experiments. Certainly all the cadmium retained could not be recovered by analysis since some must have been excreted. Even if we assume that 50 per cent. of the inspired cadmium was retained, which represents a very small amount (3 to 6 mg.), this was sufficient to cause considerable damage to important organs in these animals, namely, the lungs, liver, and kidneys.

TABLE 3.—THEORETICAL AMOUNT OF CADMIUM INSPIRED AND PERCENTAGE RETENTION IN CATS POISONED WITH LESS CONCENTRATED CADMIUM OXIDE FUME

CAT NO.	WEIGHT OF CAT	THEORETICAL AMOUNT OF CADMIUM INSPIRED	TOTAL CADMIUM FOUND	PERCENTAGE RETENTION
	kg.	*mg.*	*mg.*	
3	2.45	8.75	1.49	17.03
4	1.70	6.05	1.80	29.75
5	3.55	12.60	2.79	22.14

Cadmium Oxide Dust

For the purpose of poisoning cats with commercial cadmium oxide dust, a modification of the apparatus described by Jötten and Arnoldi (7) was used (see Fig. 5). The cats were put in the lateral branch boxes of this apparatus. The cadmium oxide was placed below in a glass tube, with a sieve at the bottom, and the glass tube connected with a blower interrupted about forty times per minute. This air blast maintained a fairly constant concentration of cadmium oxide dust in the air. Two cats were used for the experiment: Cat 6, which was exposed for twenty minutes and was killed by ether and bleeding one month later; and Cat 7, which was exposed three times—for eleven minutes on the same day as Cat 6, for fifteen minutes one month later, and for thirty minutes on the following day—and was killed by ether and bleeding six hours after the last exposure.

Symptoms.—Cat 6 had abundant salivation when removed from the box, appeared very depressed, refused to eat, and did not react to normal stimuli. Respiration was increased. During the following days the cat was very sick, had noisy respiration, and refused to eat. Seven days after exposure it showed signs of recovery, and on the eighth day began eating. During this period its weight dropped from 4.9 kg. to 2.05 kg. The symptoms shown after this exposure were similar to those following exposure to cadmium oxide fumes; therefore the

cat was left to recover, and on the following days it improved steadily although the rate of respiration continued to be higher than before the exposure. In two weeks there was an increase in weight of 0.6 kg., but this was followed by a loss during the next two weeks, so that one month after exposure, when the cat was killed, it weighed 2.3 kg.

Cat 7 showed very few symptoms following the first exposure—chiefly slight loss of appetite on the day of exposure. On the next day its appearance was absolutely normal. During the following month it gained 0.5 kg. in weight, and at the end of that time was again exposed for fifteen minutes. This second exposure apparently disturbed the cat very little, and on the following day it was again exposed for thirty minutes. After the third exposure there was abundant salivation and vomiting. Respiration was very difficult and the animal was in the same serious condition as the two cats exposed to high concentrations of cadmium oxide fume.

Autopsy.—In Cat 6 the lungs were of a light pink color, with a gray alveolar design. The trachea was normal in appearance. The liver was yellowish brown, friable on section, and had a fatty appearance. The other organs were normal. In Cat 7 the lungs were very congested, and on section exuded an aerated liquid. The trachea and other organs were normal.

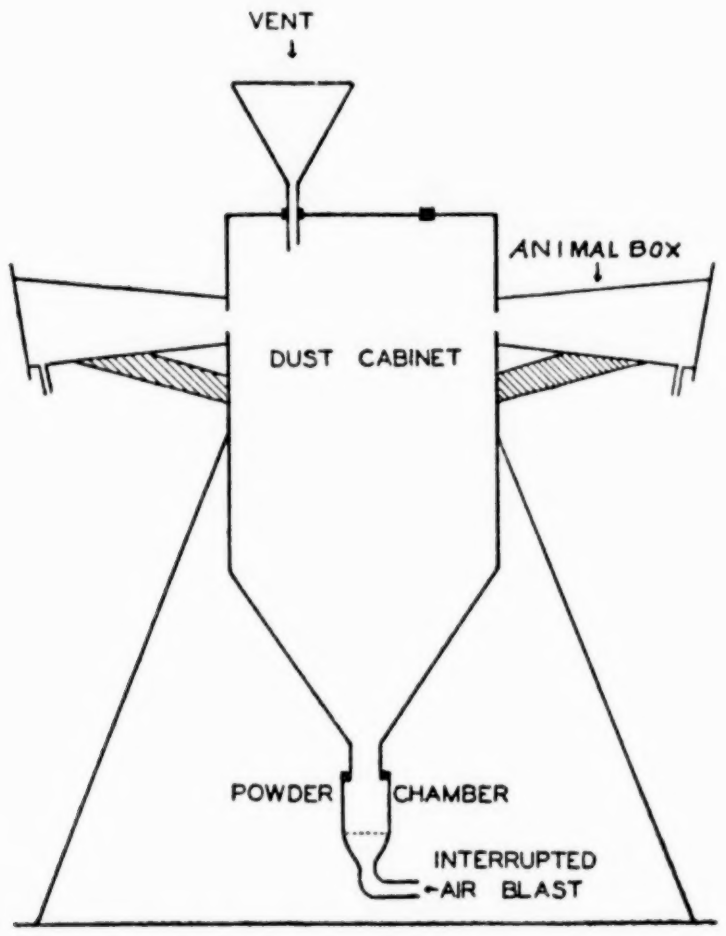

FIG. 5.—Cross section of apparatus used for poisoning cats with cadmium oxide dust and cadmium sulphide dust.

Microscopic Findings.—Cat 6 showed most pronounced changes in the lungs: chronic and subacute interstitial pneumonia, and marked thickening and fibrosis of the alveolar walls. Some hemorrhage, as well as foci of lymphoid cell infiltration, was seen. Scattering of polymorphonu-

clear leukocytes, hyperplastic alveolar epithelium, and emphysematous regions alternating with atelectatic regions were also observed. The liver showed a marked, central fatty infiltration, with an occasional tiny nec-

TABLE 4.—CADMIUM CONTENT OF TISSUES OF CAT 6, EXPOSED TO CADMIUM OXIDE DUST FOR TWENTY MINUTES AND KILLED ONE MONTH LATER

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM IN 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	80.5	0.00	0.00	0.00
Lungs	24.0	0.25	1.04	11.74
Liver	72.0	0.50	0.69	23.47
Kidneys	11.0	0.55	5.00	25.82
Bile	2.0	0.05	2.50	2.35
Urine	4.0	0.06	1.50	2.82
Heart	11.0	0.04	0.36	1.88
Spleen	2.5	0.05	2.00	2.35
Pancreas	6.6	0.08	1.21	3.75
Brain	19.5	0.05	0.26	2.35
Muscle	56.0	0.10	0.18	4.70
Bone (2 femurs)	18.0	0.40	2.21	18.77
Total	....	2.13	....	100.00

TABLE 5.—CADMIUM CONTENT OF TISSUES OF CAT 7, EXPOSED TO CADMIUM OXIDE DUST FOR ELEVEN MINUTES, AND AGAIN FOR FIFTEEN AND THIRTY MINUTES, RESPECTIVELY, ON TWO SUCCESSIVE DAYS ONE MONTH LATER

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM IN 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	73.0	traces	.....	.....
Lungs	23.0	2.00	8.70	47.96
Liver	74.0	0.75	1.11	17.99
Kidneys	20.0	0.50	2.50	11.99
Bile	2.0	0.30	1.50	7.19
Urine	1.5	0.25	16.65	5.99
Heart	8.5	0.10	1.12	2.40
Spleen	4.0	0.12	3.00	2.88
Pancreas	9.0	0.15	1.67	3.60
Total	....	4.17	.....	100.00

rotic area, and some yellow-brown material (bile or blood) in the phagocytic cells. The kidneys showed fatty infiltration, especially in the convoluted tubules. The other organs were negative. The chemical analysis of Cat 6 is given in Table 4.

The lungs of Cat 7 showed acute edema and generalized bronchopneumonia, polymorphonuclear leukocytes in the alveolar walls and alveolar lymphatics, interstitial edema, blood in some of the larger bronchioles, and acute alveolar emphysema. As was stated before, Cat 7 appeared absolutely normal following the first exposure, but lesions were found in the lungs which showed that this first exposure had had a damaging effect. Reparative reaction was found around and in the lining of the alveolar ducts. Here and there were small scars with lymphoid infiltration. The kidneys showed a moderate fatty infiltration in the tubules. The spleen showed abnormal congestion and many polymorphonuclear leukocytes. The liver and other organs were negative. The results of the chemical analysis of this cat are given in Table 5.

Discussion:

From these observations we may conclude that cadmium oxide dust is harmful, and that the toxicity resembles that of cadmium oxide fume.[1] Further, it is apparent that owing to fibrotic process, the pneumonia and bronchopneumonia produced by cadmium oxide (fume or dust) permanently damage the lungs by thickening the alveolar walls. It is important that very small amounts of cadmium oxide were capable of producing scars in the lungs, though the animal was very little disturbed by the exposure. The effect of cadmium oxide dust on the liver and kidneys was similar to that of cadmium oxide fume. One month after exposure there was a large quantity of cadmium in the body, the largest amounts being retained in the kidneys, liver, and bones.

The cadmium oxide dust concentration to which the cats were exposed, was determined and was found to be 0.4 mg. per liter of air (or 400 mg. per cubic meter of air). Taking the quantity of air inspired as 300 c.c. per kilo of cat, we have the results shown in Table 6.

[1] In the case of both cadmium oxide fume and cadmium oxide dust the amounts inhaled were very large, larger probably than would ever be encountered industrially. The experiments show that cadmium is a dangerous substance and that the type of damage to be expected is of such critical nature as to indicate the avoidance of the inhalation or ingestion of even small amounts of cadmium.

Cadmium Sulphide

The same apparatus was used as for the experiments with cadmium oxide fume. The total number of cats exposed was four: Cat 8, which was exposed for two hours and killed by ether four hours later; Cat 9, which was exposed for one hour and died one week later; Cat 10, which was exposed for two hours and twenty minutes and died on the sixth day after exposure; and Cat 11, exposed for twenty minutes and killed one week later.

Symptoms.—Cat 8 did not show the least disturbance after exposure to cadmium sulphide dust, and immediately started to eat. Cat 9 presented a normal appearance and ate well at the end of exposure and on the day following. On the third day it had

very little appetite, appeared depressed, and had diarrhea. During the following four days, until its death, it refused to eat and was very sick, showing definite pulmonary symptoms: increased rate of respiration, dyspnea, and noisy respiration. Cat 10 displayed similar symptoms, followed by death on the sixth day. In Cat 11 no symptoms were manifested following exposure. On the next day, however, the animal refused salmon and drank only milk, after which salivation appeared. On the third day salivation continued and vomiting occurred in the afternoon after drinking milk. On the fourth day the cat appeared depressed, was dyspneic, and took only a very little milk and salmon. These conditions continued for several days but the cat was not so seriously sick as Cats 9 and 10.

Autopsy.—The lungs of Cat 8 were normal in appearance except for numerous dark spots denoting areas of atelectasis. The lungs of Cat 11 were nearly normal, having little congestion. Cats 9 and 10 showed considerable congestion. In the rest of the organs nothing abnormal was observed.

Microscopic Findings.—In Cat 8 the lungs showed extensive emphysema, some alveolar edema, extensive interstitial and alveolar hemorrhage, and early pouring out of polymor-

TABLE 6.—THEORETICAL AMOUNT OF CADMIUM INSPIRED AND PERCENTAGE RETENTION IN CATS POISONED WITH CADMIUM OXIDE DUST

CAT NO.	WEIGHT OF CAT	TIME EXPOSED	CADMIUM CONTENT OF AIR	THEORETICAL AMOUNT OF CADMIUM INSPIRED	TOTAL CADMIUM FOUND	PERCENTAGE RETENTION
	kg.	*min.*	*mg./l.*	*mg.*	*mg.*	
6	4.9	20	0.4	11.76	2.13	18.11
7	2.0	11	0.4	2.64		
		15	0.4	3.60	4.17	31.03
		30	0.4	7.20		
				Total 13.44		

TABLE 7.—CADMIUM CONTENT OF LUNGS AND LIVER OF CAT 8, POISONED BY INHALATION OF CADMIUM SULPHIDE

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM IN 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Lungs	16.0	1.95	11.86	92.86
Liver	62.0	0.15	0.32	7.14
Total	....	2.10	.....	100.00

phonuclear leukocytes. The observation gave the impression that the extensive acute emphysema might be due to the obstruction of the small bronchioles and alveolar ducts by the cadmium sulphide dust. Chemical analysis is given in Table 7.

The lungs of Cat 9 showed marked engorgement of the blood vessels and capillaries, with hemorrhage in the interstitial tissue and alveoli. There was extensive emphysema, some atelectasis, but relatively little inflammatory cell infiltration and edema. The liver and kidneys were very little involved.

Examination of the lungs of Cat 11 showed moderate congestion, quite extensive interstitial and alveolar hemorrhage, and early pouring out of the polymorphonuclear leukocytes. There was moderate emphysema and atelectasis.

Discussion:

From these observations we may conclude that cadmium sulphide is far from being harmless. Its noxious action is different from that of cadmium oxide. The subjective symptoms, usually appearing from twenty-four to thirty-six hours after exposure, are vomiting and diarrhea, occasionally salivation, dyspnea, and noisy respiration. The pathologic changes referable to cadmium itself take place slowly. The first change in the lungs is an extensive emphysema, which cannot be other than mechanical, resulting from the filling of the small bronchioles and alveolar ducts with cadmium sulphide dust. This effect is of course not specific for cadmium. After thirty-six to forty-eight hours the animals develop generalized pneumonia, and bronchopneumonia with edema, and after about a week they die. Very small amounts of cadmium sulphide are capable of producing congested inflammatory conditions in the lungs, and this can occur without antecedent atelectasis or emphysema. The fact that even one week after exposure to cadmium sulphide dust over 70 per cent. of the total cadmium found was in the lungs, explains why the other organs were affected very little, if at all. The difference in the action of cadmium sulphide and cadmium oxide is due to the difference in physicochemical properties. Cadmium sulphide, being very insoluble, is resorbed slowly; therefore the subjective symptoms are retarded and its distribution in the body is limited. Because of its lower density, it requires a greater volumetric amount than cadmium oxide, and consequently the tendency to emphysema production is greater.

Poisoning by Feeding

Cadmium poisoning through the gastro-intestinal tract, as has already been mentioned, is of no great practical importance for man. The aim was especially to investigate microscopically the pathologic changes which were observed macroscopically in poisoning by feeding, and also to determine the distribution of cadmium in the body.

For this purpose two cadmium compounds were used, namely, cadmium carbonate and cadmium phosphate. We had three groups of cats, with two in each group, for each salt, and two cats as control animals, making a total of fourteen. The cadmium salts were suspended in a 2 per cent. solu-

tion of gum acacia, of which 1 c.c. was equivalent to 10 mg. of metallic cadmium. The cats were fed with salmon and milk to which the cadmium was added in different doses for each group. Feedings were given daily except Sundays for the first month, and every day including Sundays during the second month, with the exception of Christmas day.

The cats were weighed, and blood samples were taken, before the experiment was started and every two weeks afterwards. At the end of the observations the animals were killed by bleeding; specimens were then taken for microscopy, and the body was analyzed for cadmium. The aim was to make the cats eat all the cadmium destined for them, and this was accomplished for the most part except in the case of the highest doses. An estimate was made of the consumed food containing cadmium, but no attempt was made to determine how much was vomited. As there was no difference between the effects of the two cadmium salts, the observations will be described together.

Table 8 shows the grouping of the cats according to the amount and the duration of cadmium feeding: Group A, fed 100 mg. daily for one month; Group B, 10 mg. for two months; and Group C, 2 mg. for two months.

TABLE 8.—GROUPING OF CATS FED DIFFERENT AMOUNTS OF CADMIUM CARBONATE AND CADMIUM PHOSPHATE

GROUP	CAT NO.	COMPOUND FED	DOSE DAILY	DURATION OF FEEDING	KILLED AT END OF FEEDING	KILLED 1 MO. AFTER FEEDING DISCONTINUED
			mg.	*mos.*		
A	1	$CdCO_3$	100	1	yes	...
	2	$Cd_3(PO_4)_2$	100	1	yes	...
	3	$CdCO_3$	100	1	...	yes
	4	$Cd_3(PO_4)_2$	100	1	...	yes
B	5	$CdCO_3$	10	2	yes	...
	6	$Cd_3(PO_4)_2$	10	2	yes	...
	7	$CdCO_3$	10	2	...	yes
	8	$Cd_3(PO_4)_2$	10	2	...	yes
C	9	$CdCO_3$	2	2	yes	...
	10	$Cd_3(PO_4)_2$	2	2	yes	...
	11	$CdCO_3$	2	2	...	yes
	12	$Cd_3(PO_4)_2$	2	2	...	yes

Group A

Of the four cats in this group, two (Cats 1 and 2) were killed by bleeding after one month of cadmium feeding, and two (Cats 3 and 4) were allowed to live for one month following the feeding experiment, during which time they were given only salmon and milk.

Symptoms.—During the entire feeding period there was always vomiting when the cats ate food containing 25 per cent. or more of cadmium. At the beginning of the experiment the vomiting occurred within from two to four

hours after the meal; later it was delayed so that at the end of about a month it occurred from eighteen to twenty-four hours after eating. In these cases of delayed vomiting the food was very little digested, having almost the same appearance as in the period of early vomiting. This is perhaps explained by the toxic effect of the cadmium salts on the gastric ferments. At the beginning of the feeding the vomiting was preceded by abundant salivation, and this still persisted after the vomiting. The cats, as would be expected, lost considerable body weight during the cadmium feeding. This may be explained by the inanition due to vomiting, loss of appetite, and deficient digestion of the retained food, and also to the toxic effect of cadmium. When the cadmium was discontinued the animals ate better and partly regained their lost weight.

Autopsy.—In Cat 1 the kidneys had the aspect of the so-called "big white kidney." The lungs, liver, and other organs were normal in appearance. Cats 3 and 4 showed nothing abnormal, and Cat 2 nothing except possibly a fatty liver and large kidneys.

Microscopic Findings.—Cat 1 showed very slight congestion of the lungs, a few polymorphonuclear cells in the alveolar walls, and some emphysema. The liver was essentially negative. The kidneys showed a varying degree of degeneration of the tubular epithelium, involving principally the proximal convoluted tubules, and to a slight extent the collecting tubules. The glomeruli showed no change. The gastro-intestinal tract, the trachea, and other organs, including the heart,

TABLE 9.—CADMIUM CONTENT OF TISSUES OF CAT 1, FED 100 MG. OF CADMIUM CARBONATE DAILY FOR ONE MONTH AND KILLED AT END OF CADMIUM FEEDING

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM PER 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	97.5	0.00	0.00	0.00
Lungs	21.5	0.10	0.46	0.83
Liver	67.5	6.75	10.00	55.97
Kidneys	44.0	4.00	9.10	33.17
Bile	2.0	0.12	6.00	1.00
Urine	8.0	0.10	1.25	0.83
Heart	14.0	0.10	0.71	0.83
Spleen	7.5	0.05	0.67	0.41
Pancreas	7.0	0.05	0.71	0.41
Brain	22.0	0.07	0.32	0.57
Muscle	67.0	0.12	0.18	1.00
Bone (2 femurs)	28.5	0.60	2.10	4.98
Total	....	12.06	.....	100.00

spleen, pancreas, brain, bone marrow, and muscle, were all negative. The chemical analysis of this cat is given in Table 9. The analysis of 11 gm. of feces (found in the rectum) yielded 60 mg. of cadmium.

The lungs of Cat 2 showed very few polymorphonuclear cells. In the liver there was a general granulation of the cells, which was more prominent in the central areas. The kidneys presented the same tubular fatty degeneration as those of Cat 1, but to a lesser extent.

Blood Changes.—The blood was not affected in this group of feeding experiments.

Group B

The cats in this group were fed 10 mg. of cadmium daily for two months, after which two (Cats 5 and 6) were killed and two (Cats 7 and 8) were put on a plain diet for a month.

Symptoms.—During the first ten or twelve days vomiting occurred from four to six times, accompanied by salivation. During the vomiting period the appetite was decreased. After vomiting ceased, all the cats started to eat well, and continued to do so until about the end of the second month when, with the exception of Cat 5, they all showed a marked decrease in appetite. Cat 5 refused to eat on the forty-second day of the cadmium feeding, and was killed the next day. The variations in body weight were definite only for Cat 5, in which there was a steady decrease.

TABLE 10.—CADMIUM CONTENT OF TISSUES OF CAT 3, FED 100 MG. OF CADMIUM CARBONATE DAILY FOR ONE MONTH AND KILLED ONE MONTH AFTER DISCONTINUANCE OF CADMIUM FEEDING

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM PER 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	117.0	0.00	0.00	0.00
Liver	103.0	4.00	3.88	57.14
Kidneys	38.0	2.00	5.26	28.57
Bile	0.8	0.05	6.25	0.72
Urine	34.0	0.15	0.44	2.14
Bone (1 femur)	16.0	0.80	5.00	11.43
Total	.....	7.00	....	100.00

In Cat 3 the lungs were negative; the liver showed a general granulation of the cells, and large vacuoles of fat. The fat accumulation was not so prominent in the central areas, but seemed to be more generalized. If there was any repair it was very slow. The kidneys showed a pronounced fatty degeneration of the tubules. Chemical analysis of the tissues is given in Table 10.

The changes observed in Cat 4 were much the same as those in the other cats in this group.

Autopsy.—Except for a very fatty

liver in Cat 5, nothing abnormal was found.

Microscopic Findings.—In Cat 5 the liver showed a strikingly profound alteration, so that the central and midzonal areas of lobules stood out prominently as lightly stained vacuolated areas. In the periphery of the lobules of the liver the tissue was relatively normal in all respects. The portal blood vessels and biliary ducts presented no abnormalities. The central veins were engorged. A more detailed study of the central areas mentioned above revealed that practically every liver cell contained many small or single large, clear vacuoles of fat. This fat accumulation caused distortion of the columns of liver cells so that the sinusoidal spaces were difficult to recognize and appeared compressed. Throughout the liver tissue, but especially near the periphery of the lobules, a yellow-brown pigmented material was noticed in the form of droplets and granules, often enclosed within phagocytic cells. Occasional scattered liver cells could be seen which were necrotic and were invaded by polymorphonuclear leukocytes. The kidneys showed a moderate degree of fat in the tubules; the other organs were negative. The chemical analysis of Cat 5 is given in Table 11. The analysis of the feces showed 10 mg. of cadmium in 6 gm. of feces.

TABLE 11.—CADMIUM CONTENT OF TISSUES OF CAT 5, FED 10 MG. OF CADMIUM CARBONATE DAILY FOR TWO MONTHS AND KILLED AT END OF CADMIUM FEEDING

TISSUE	WEIGHT OF TISSUE	TOTAL CADMIUM FOUND	CADMIUM PER 100 GM. OF TISSUE	PERCENTAGE OF TOTAL CADMIUM FOUND
	gm.	*mg.*	*mg.*	
Blood	62.0	0.00	0.00	0.00
Lungs	14.0	0.10	0.79	2.16
Liver	44.5	2.50	5.62	54.11
Kidneys	21.5	1.00	4.65	21.65
Bile	1.5	0.07	4.66	1.52
Urine	11.0	0.15	1.36	3.25
Heart	9.0	0.05	0.56	1.08
Pancreas	5.0	0.04	0.80	0.87
Spleen	4.5	0.05	1.11	1.08
Brain	23.0	0.06	0.26	1.30
Muscle	99.0	0.10	0.10	2.16
Bone (2 femurs)	20.0	0.50	2.50	10.82
Total	....	4.62	....	100.00

The changes observed in the other cats in this group consisted chiefly in granulation of the liver cells and pronounced fatty degeneration of the renal tubules.

Blood Changes.—No marked blood changes were noted except in Cat 5,

which showed an increase in the number of red cells and in the hemoglobin content.

Group C

The experiments in this group, in which cats were fed 2 mg. of cadmium daily for two months, proved to be simple variants of those with large doses, and they will therefore not be considered separately.

Discussion:

Cats fed with large doses (100 mg.) of cadmium vomited during the entire period of cadmium feeding. At the beginning of the period the vomiting occurred within two or three hours after eating, but it became progressively delayed until at the end it occurred from eighteen to twenty-four hours after eating. The cats showed a marked loss of appetite and a progressive loss of weight. The loss of weight was so pronounced in one instance (Cat 1) that the muscles were reduced to a minimum and the cat could hardly walk. The cats which were fed an intermediate dose (10 mg.) vomited only at the beginning of the period. They lost less weight than the animals fed larger doses, and had fairly good appetites except during the vomiting period and at the end of the second month. The vomiting in both groups of cats was accompanied by salivation. The cats fed with small doses (2 mg.) did not vomit, and in general maintained their body weight. Their appetites were good except at the end of the second month, when there was a marked loss of appetite. During the feeding period no other symptoms were observed.

At autopsy, in general no pathologic changes were found except occasionally very marked fatty liver and large kidneys. The urine from these cats gave a typical Gmelin test, and was negative for albumin when tried in a few cases (four in all). Microscopic changes occurred chiefly in the liver and the kidneys, and in such a manner that either one or the other was more affected, and only seldom were both affected profoundly. For the most part, the cats with less appetite, or those that refused more often to eat, had badly affected livers; in those that ate well, the kidneys were more affected. The changes in the liver ranged from general granulation of the liver cells, as the minimum, to a generalized fatty infiltration as the most profound change, predominant in the central areas of liver lobules. The cats which were put on a plain diet for one month after the cadmium feeding was discontinued did not show any sign of repair; if there was any it was very slow. The changes in the liver were accompanied by a biliary stasis. The kidneys presented only one type of lesion, namely, fatty infiltration, which was more predominant in the convoluted tubules and occurred very little in the collecting tubules; the remainder of the kidneys was more or less normal in appearance. No casts were observed in the tubules, such as were described by Severi (8) after intravenous injection of cadmium chloride. Neither was inflammation of the upper respiratory tract observed during the period of cadmium feeding, as described by Schwarz and Otto (9), and the microscopy of the trachea was always negative. The gastrointestinal tract also appeared normal

in all instances, both macroscopically and microscopically.

The cadmium was stored principally in the liver; in the majority of cases the kidneys contained the greatest relative amount (*i.e.*, the quantity per 100 gm. of tissue), and in a few cases the greatest absolute amount. The excretion was effected through the gastro-intestinal tract and the kidneys, and was very slow as is seen from the analysis of the organs of the cats remaining on a plain diet for one month after cadmium feeding was discontinued. The blood did not change in any definite way.

The observations concerning vomiting and distribution of cadmium in the body are in accordance with Schwartze and Alsberg's (10) findings, and the distribution of cadmium is also in accordance with Hessel's (11) work, except that in neither instance (10) (11) was cadmium found in the bones.

Prevention of Poisoning

It has been shown that cadmium poisoning as an industrial hazard occurs through the respiratory tract, and that very small amounts of cadmium oxide fume or dust, as well as of cadmium sulphide, may produce serious damage in the lungs. On the basis of these observations one may conclude that cadmium, no matter how small the amount taken into the lungs, causes pathologic changes, and that there is, therefore, no permissible amount of cadmium.

There are two possible methods for protection against cadmium fume or dust: adequate ventilation at the source of the fume or dust, which is of course the more important; and the provision of masks or respirators for use in emergencies or for short periods of time. The type of ventilation which should be provided will not be discussed here, but the protective value of one type of mask and one type of respirator will be presented, together with suggestions as to when each should be used.

The Burrell dust mask and the Willson bag respirator were tested for cadmium oxide fume and for cadmium chloride fume mixed with hydrochloric acid. The procedure was as follows: Cadmium was burned in an electric furnace in a large dust cabinet. After there was sufficient cadmium oxide fume, samples were taken with two impingers in series (12) for the determination of the cadmium concentration in the cabinet. Air was then extracted from the cabinet through the respirator or the mask, and conducted through the double impinger, in order to determine the cadmium content. Finally, from the cadmium concentration in the cabinet and the quantity of cadmium passed through the mask or the respirator, the percentage efficiency of each device was calculated. For the tests with cadmium chloride fume, cadmium chloride was burned in an electric furnace, and in order to simulate industrial conditions hydrochloric acid vapor was introduced, the concentration of which was not determined since cadmium chloride and hydrochloric acid in varying amounts sometimes occur together in industry. The determination of the cadmium content of the cabinet and the test for the masks were carried out in the same way as for cadmium oxide.

The results of these tests, presented

in Table 12, show that the Burrell dust mask retained a greater percentage of cadmium than the Willson bag respirator. A respirator of the efficieney of the Willson bag seems suitable for protection against low concentrations, while the Burrell mask is advisable when high concentrations are encountered. It should be emphasized again, however, that adequate ventilation is the chief consideration in protective measures. Furthermore, persons who have once been exposed to cadmium in any form and have developed pulmonary symptoms, however mild, should not suffer a second exposure. In the smelting of zinc ores containing cadmium, particular precaution should be taken during the first two hours when cadmium fume in high concentration is given off. The possibility of cadmium poisoning in zinc smelters was asserted by Tracinski (13) and Sigel (14), and more recently by

TABLE 12.—EFFICIENCY OF BURRELL DUST MASK AND WILLSON BAG RESPIRATOR IN CADMIUM OXIDE FUME AND IN CADMIUM CHLORIDE FUME MIXED WITH HYDROCHLORIC ACID

COMPOUND	CADMIUM CONCENTRATION IN CABINET	MASK OR RESPIRATOR TESTED	PERCENTAGE EFFICIENCY
	mg./cu. m.		
Cadmium oxide	134.00	Burrell mask	96.2
	55.00	Willson bag	79.0
	26.00	Willson bag	82.6
Cadmium chloride	19.30	Willson bag	73.3
	11.00	Burrell mask	82.5
	8.84	Willson bag plus soda lime cartridge[1]	87.0

[1] The soda lime cartridge is for protection against the hydrochloric acid vapors.

FIG. 6.—Particles of cadmium oxide fume. × 1,285.

Stephens (15). Stephens based his conclusions on chemical analyses made on the livers of persons working in zinc smelting.

The fact that the efficiency of the mask and the respirator is not nearer 100 per cent. is probably explained by the smallness of the cadmium oxide fume particles. A measurement of these particles after the fume had been set up eight hours showed that 83.5 per cent. were under 1 micron. The sample was taken with the electric precipitator, and the floccules were left out of the measurement. The appearance of the cadmium oxide fume is given in Figure 6. The size of particles reported by Legge (16) shows 96 per cent. under 2 microns. The smallness of the particles is an additional argument for adequate ventilation.

Summary and Conclusions

A thorough review of the literature showed that the work done on cadmium was considerably varied, but unsatisfactory from the standpoint of the industrial hygienist (17). Although industrial cadmium poisoning occurs practically entirely through the respiratory system, the least work was done in this direction. Even in feeding experiments the pathologic changes were not precisely determined since they were not verified by microscopic examination. Much has been achieved, therefore, in the present study which presents valuable information for the industrial hygienist.

Poisoning by Inhalation

Cadmium poisoning was produced in cats through the respiratory system with cadmium oxide fume, cadmium oxide dust, and cadmium sulphide dust. From these experiments the following conclusions may be drawn:

Cadmium Oxide Fume and Dust.—Cadmium oxide fume or dust when inhaled produces an increase in the rate of respiration and abundant salivation, which appears during the exposure or immediately after. Later the respiration becomes more dyspneic and noisy. The animals refuse entirely to eat or drink.

In high concentrations cadmium oxide induces the development of edema of the lungs which results in the death of the animals. In smaller amounts it produces generalized pneumonia and bronchopneumonia, emphysema, and atelectasis. The development of the pneumonia is accompanied by a progressive thickening of the alveolar walls constituting a permanent damage due to fibrotic tissue and indicated by the subjective symptom of increased rate of respiration. The emphysema at best is partly mechanical, being formed by filling of the small bronchioles and alveolar ducts with cadmium oxide. In very small amounts cadmium oxide produces scars in the lungs, though there are no subjective symptoms following such exposures.

Cadmium oxide produces changes in the liver varying from a general granulation of the cells, as a minimum lesion, to a pronounced fatty infiltration of the cells from the central areas of the lobules, as a maximum lesion. The kidneys are affected by a fatty infiltration of the cells which is more pronounced in the convoluted tubules. The other organs in general are not affected.

Cadmium is found mainly in the

lungs, liver, and kidneys shortly after the exposure; later it becomes stored up chiefly in the liver, kidneys, and bones.

Cadmium Sulphide Dust.—The animals exposed to cadmium sulphide dust manifested symptoms only after twenty-four to thirty-six hours following the exposure. These consisted in vomiting, diarrhea, occasional salivation, and increased rate of respiration, which was dyspneic and noisy.

Cadmium sulphide causes generalized pneumonia and bronchopneumonia accompanied by edema, and extensive emphysema and atelectasis of a mechanical nature. The lungs are usually the only organs affected.

Cadmium is found mainly in the lungs, with a small percentage in the liver and kidneys. The difference in the distribution of cadmium sulphide and cadmium oxide is explained by the greater insolubility of the former compound.

With both cadmium sulphide and cadmium oxide the excretion is affected very slowly through the kidneys and the gastro-intestinal tract. No definite blood changes are found.

Poisoning by Feeding

Cadmium poisoning was produced by feeding cats cadmium carbonate and cadmium phosphate. Since no difference was noted in the action of these two salts, the same conclusions may be drawn from both groups of experiments:

Cadmium fed in large doses induces vomiting, with salivation and loss of appetite. Vomiting also occurs for a short period following medium doses, but is absent with small doses. The vomiting and loss of appetite are followed by loss of body weight.

Irrespective of the dose of cadmium fed, the liver and kidneys are affected, with more pronounced lesions in one or the other. The liver presents changes varying from a general granulation of the cells to a pronounced fatty infiltration, especially around the central vein. The kidneys show a fatty infiltration, which is more prominent in the convoluted tubules. The other organs are not usually affected.

Cadmium is retained in the liver in greater absolute quantity, and in the kidneys in greater relative quantity. The bones also retain a high percentage.

Cadmium is excreted very slowly through the kidneys and the gastro-intestinal tract.

No definite blood changes are found.

Prevention of Poisoning

One type of mask and one type of respirator were tested against cadmium oxide and against cadmium chloride mixed with hydrochloric acid vapor. The use of the respirator is recommended where the percentage of cadmium contained in the material handled is small. A soda lime cartridge should be attached to the respirator when acid fume is also present in the atmosphere. The mask should be used in all cases where the cadmium content is high. Adequate ventilation is the most important consideration in the prevention of cadmium poisoning.

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THE REACTIONS OF THE ORGANISM TO REPEATED ELECTRIC SHOCKS*

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IN order to obtain chronic and well-marked pathologic lesions in the nervous system, it was proposed to follow the technic of Morrison, Weeks, and Cobb (1) and subject rats to a series of electric shocks. When this work was begun, one unusual observation claimed the attention of the experimenters and led to the studies presented here. It was found that the animals which survived the initial shock were less affected by subsequent shocks.

In these experiments the technic was essentially the same as that reported by the authors in previous papers. Rats were again used as the experimental animals and were given ether until they were quite unconscious during the period of the shock. The current supply was a 60-cycle alternating current circuit and means were provided for varying the voltage over a wide range. The two contacts with the electric circuit were made on the dorsal surface of the head and at the base of the tail.

EXPERIMENTAL FINDINGS

Table 1 shows the effects of repeated electric shocks upon twenty-five rats; the survivors received twelve shocks at approximately three-day intervals. The duration of each shock was the time required to close and open the switch, approximately two-tenths of a second. The initial shocks were given at 248 volts; when repeated shocks at this potential ceased to have any injurious effect upon the survivors, the voltage of the circuit was raised. The results of the injury to the animals is recorded under four headings in Table 1: those that died at once, those that were paralyzed, those that recovered completely from the immediate effects of the shock, and those that died in the interval between the experimental periods. As has been stated in previous reports, the rats which show paralysis of the hind legs following a shock will not survive. These animals were therefore killed as soon as the paralysis was manifest. It is clear, then, that the rats lost from the series after each shock represent the sum of those that died at once or in the interval and those that were paralyzed.

No rats were killed but four were paralyzed by the first contact with a circuit at 248 volts. The second shock at the same voltage paralyzed two, and the third and fourth shocks each one. One died in the interval between the third and fourth experiments. After the fourth shock, however, none of the

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survivors were paralyzed by the next eight contacts, although the voltage of the circuit was raised until it reached 1,200 in the last two experiments. The first immediate death occurred following the eleventh shock, at 1,200 volts, but there was one interval death after the fourth exposure to a circuit at 500 volts. The first shock at 1,200 volts, the eleventh shock that the animals had received, caused one immediate death and three deaths in the interval. The second 1,200-volt shock resulted in four immediate deaths. The series was stopped at this point, and the remaining animals included in the group are discussed in Table 2.

TABLE 1.—EFFECTS OF REPEATED ELECTRIC SHOCKS ON TWENTY-FIVE RATS

Shock was instantaneous

NO. OF SHOCKS	DATE 1931	VOLTAGE	NO. OF RATS	DIED	PARALYZED	RECOVERED	DEATHS IN INTERVAL
1	9/18	248	25	0	4	21	0
2	9/21	248	21	0	2	19	0
3	9/23	248	19	0	1	18	1
4	9/25	248	17	0	1	16	0
5	9/28	248	16	0	0	16	0
6	9/30	248	16	0	0	16	0
7	10/2	500	16	0	0	16	0
8	10/4	500	16	0	0	16	0
9	10/7	500	16	0	0	16	0
10	10/11	500	16	0	0	16	1
11	10/18	1,200	15	1	0	14	3
12	10/24	1,200	11	4	0	7	0

From Table 1 certain facts suggest themselves which may be stated as follows: If a group of rats are shocked from a low circuit, a certain number of them are paralyzed following the first shock and a decreasingly small number during subsequent shocks until a point is reached where no further injury takes place at the low voltage. If the voltage of the circuit is then doubled or even quadrupled, no further cases of paralysis occur, although deaths immediately following the shocks occur with the high voltage.

These facts are demonstrated in an even more striking way in Table 2, which shows the results of experiments with 111 rats, including the twenty-five presented in Table 1. In this series four rats died after the first shock at 248 volts and one rat following the third shock at the same voltage. No further deaths occurred at 248 volts, but when the voltage was raised, deaths immediately after the experiment and interval deaths became numerous. Twenty-two rats were paralyzed following the first shock; the cases of paralysis decreased to ten at the second, two at the third, and four at the fourth shock. No further cases occurred until the thirteenth exposure, when the voltage was dropped to 52 volts, which was about one-fifth of the voltage used at the beginning of the series. The duration of the contact was now increased to two seconds. No deaths immedi-

ately following the shock occurred, but paralysis reappeared and two rats were paralyzed after the first shock and one after the second. Another animal was paralyzed after a two-second shock from a circuit at 250 volts, the initial voltage of the series. When the voltage was raised again to 500, one rat died immediately following the shock.

TABLE 2.—EFFECTS OF REPEATED ELECTRIC SHOCKS ON 111 RATS[1]

NO. OF SHOCKS	DATE 1931	VOLTAGE	DURATION OF SHOCK	NO. OF RATS	DIED	PARALYZED	RECOVERED	DEATHS IN INTERVAL
1	9/18	248	instantaneous	111	4	22	85	2
2	9/21	248	"	83	0	10	73	0
3	9/23	248	"	73	1	2	70	1
4	9/25	248	"	69	0	4	65	2
5	9/28	248	"	63	0	0	63	0
6	9/30	248	"	63	0	0	63	0
7	10/2	500	"	63	1	0	62	0
8	10/4	500	"	62	6	0	56	1
9	10/7	500	"	55	1	0	54	0
10	10/11	500	"	54	0	0	54	4
11	10/18	1,200	"	50	7	0	43	8
12	10/24	1,200	"	35	5	0	30	2
13	10/28	52	2 seconds	28	0	2	26	2
14	11/4	52	" "	24	0	1	23	1
15	11/7	52	" "	22	0	0	22	2
16	11/12	125	" "	20	0	0	20	2
17	11/15	250	" "	18	0	1	17	2
18	11/22	500	" "	15	1	0	14	2

[1] Includes rats presented in Table 1.

The latter experiments suggest that paralysis is more common at low voltage circuits inasmuch as it reappeared in the series when the voltage was dropped from a high to a low level. It must be remembered, however, that the duration of the shock was increased.

Another series of experiments was begun with shocks at extremely low voltage (30), with the expectation that this would do no injury to the animals and that the paralysis might be avoided if the voltage was increased gradually in subsequent experiments. The current was allowed to flow for two seconds. The results, which are given in Table 3, show that paralysis was even more marked than in the previous series. Seventeen of the forty-nine rats were paralyzed with the first shock, twelve with the second, and one with the third shock, which was from a circuit at 52 volts. There were no further cases of paralysis, but several deaths occurred immediately following the shock. Sixty-one per cent. of this series were paralyzed as the result of the first three shocks.

The question then arose as to the number of rats paralyzed by the first shock at different voltages, inasmuch as it appeared from the foregoing tables that paralysis was more common after shock from circuits at relatively low voltages. By utilizing suitable

data from previous studies and enlarging the series, it was possible to learn the number of rats that would be paralyzed out of a series of twenty, from contact with circuits at eleven different voltages. The results are given in Table 4. The first five circuits at 8 to 23 volts sent an extremely minute amount of current through the body of the animal. Under ordinary conditions, if man made contact with a circuit of 30 volts or less, he would scarcely be aware of it. No injury was evident after contact with the 8 and 13 volt circuits. Indeed, the amount of contraction of the striated musculature was slight and consisted in clonic rather than tonic contractions. With the four circuits from 15 to 30 volts, paralysis was produced in certain of the animals and tended to increase in frequency as the voltage was raised. The largest numbers of rats were paralyzed from the circuits at 125 and 250 volts; at 500 and 1,000 volts the number decreased. Deaths as immediate results of the shock occurred with circuits at 250,

TABLE 3.—EFFECTS OF REPEATED SHOCKS AT LOW VOLTAGES

Duration of shock = 2 seconds

NO. OF SHOCKS	DATE 1931	VOLTAGE	NO. OF RATS	DIED	PARALYZED	RECOVERED	DEATHS IN INTERVAL
1	10/15	30	49	0	17	32	0
2	10/18	30	32	0	12	20	0
3	10/21	52	20	0	1	19	1
4	10/24	52	18	3	0	15	1
5	10/28	126	14	1	0	13	0
6	11/4	126	13	0	0	13	2
7	11/7	252	11	0	0	11	0
8	11/12	500	11	2	0	9	2
9	11/15	30	7	0	0	7	0

TABLE 4.—EFFECTS OF FIRST SHOCK AT DIFFERENT VOLTAGES

Duration of shock = 2 seconds

VOLTAGE	NO. OF RATS	DIED	PARALYZED	RECOVERED	ARTIFICIAL RESPIRATION	EMISSION	BLEEDING
8	20	0	0	20	0	1	0
13	20	0	0	20	0	0	0
15	20	0	1	19	0	6	3
17.5	20	0	3	17	0	9	14
23	20	0	4	16	0	4	4
30	20	0	7	13	0	18	19
52	20	0	2	18	0	18	10
125	20	0	14	6	20	20	17
250	20	3	13	4	7	19	20
500	20	3	6	11	16	19	12
1,000	20	9	5	6	20	20	18

500, and 1,000 volts. Perhaps some of the rats that died immediately might have been paralyzed had they survived.

Animals show wide variation in their susceptibility to electric currents, depending on their size and weight, and particularly on their general vigor. Thus one consignment of rats received in the laboratory would be severely damaged by a shock which would not injure another group at all. This introduces a large variable factor in Table 4, where it was necessary to use rats from more than one consignment. It is felt, however, that this table gives a fair picture of the paralysis produced by contact with circuits at these different voltages, although the exact numbers paralyzed in the different groups would not be reduplicated exactly in further work.

Discussion

Perhaps the chief interest in these experiments focuses on the decrease and later absence of paralysis after a series of electric shocks at one constant voltage. This is illustrated in Tables 1 and 2 in the first six shocks from a circuit at 248 volts. The paralysis was most marked after the first shock; the paralyzed animals decreased in number after the next three shocks and none were paralyzed after the fifth and sixth shocks. Thereafter no paralysis followed four shocks from a circuit at 500 volts and two shocks from a circuit at 1,200 volts. Thirty-four per cent. of the rats were paralyzed by the first four shocks.

Several questions are raised as the result of these findings. Do all the rats that are susceptible to paralysis succumb to the first few shocks, and are the remainder naturally more resistant to this type of injury from electricity? Or do the rats acquire an immunity to electric contacts after the first few shocks? Certain arguments may be advanced upon both sides, but first the mechanism of the paralysis will be discussed.

When the spinal cord of one of the paralyzed rats is exposed, it is found to be abnormally soft. The region of the posterior columns at the upper thoracic level stains a dull purple color. Cross sections of the cord show that the lesion is usually limited to the posterior columns, although the whole cord sometimes becomes necrotic. The injured area stains a reddish color. Microscopic examination shows that the fibers of the posterior columns are completely interrupted; the area is filled with fat and necrotic débris, with a liberal sprinkling of red blood cells. If the animals are killed and examined as soon as the paralysis is manifest and frozen sections of the cord are studied microscopically, it can be seen that groups of red cells occur among masses of fat, the remains of the injured myelin sheaths. Fat stains at this time do not clarify the picture inasmuch as the myelin is not yet broken down into simpler fats that stain with sudan III or scharlach r. Moreover, the paralyzed animals can be kept alive only two or three days and therefore the late changes cannot be observed.

It was at first felt that the lesion in the cord was essentially a hemorrhagic one due to rupture of the artery in the dorsomedian septum, the blood spreading out into the posterior columns. The increase in blood pressure which follows the electric shocks and the

sudden and violent flexion of the back during the time that the current is flowing were suggested as causes of damage to the artery. The fact that the lesion always occurs in the upper thoracic region speaks against hemorrhage due to increase in blood pressure. Moreover the hemorrhages in the conjunctivae that are attributable to increased blood pressure occur with each shock, regardless of the number of previous shocks which the rat has received. The sharp localization of the lesion is in favor of an accident due to the strong contraction of the trunk musculature with unusual flexion of the back and rupture of the artery. It is difficult to see why such an accident might not occur at any time during a series of shocks. The explanation might be advanced that all the susceptible animals were injured by the first few shocks. The paralysis is quite as frequent in small and young rats as it is in old animals; one would expect it to occur most frequently in those with senile degenerative changes in the arteries.

Recently an objection has been advanced to the explanation of the paralysis primarily on the basis of a vascular lesion. It was suggested that the current itself produced trauma to the fibers of the posterior columns of the cord and that the commotion in this region caused capillary bleeding, giving the area the appearance of a vascular accident. In favor of this theory it may be said that the bleeding and damage is not so extensive as one would expect if the rather large artery in the dorsomedian septum were damaged; in section the red cells are not extremely numerous but are scattered among the fat globules. With the electrodes attached to the head and tail, the current flows along the long axis of the spinal cord and probably much of it is carried in the spinal cord itself. The central nervous system is of smallest diameter in the thoracic region and consequently the current density is concentrated at this point with resulting damage to the spinal cord.

Moreover, earlier experiments demonstrate that the current pathway is an important factor in the production of paralysis. This could scarcely be the case if the lesion were due to a rise in blood pressure or to a sudden, strong contraction of the musculature, for the effect upon blood pressure and muscular contraction should be nearly the same, whatever the pathway of the current. The differences in the frequency of paralysis with varying current pathways were shown in a group of rats subjected to a two-second shock from a circuit at 1,000 volts. Thirty-eight per cent. were paralyzed when contacts were made with the head and tail, and 8 per cent. with contacts on either foreleg and either hind leg; none were paralyzed with the contacts on the two hind legs. When the current flowed from a foreleg to a hind leg its pathway was not so well oriented in relation to the spinal cord as when it flowed from the head to the tail. In cases where the current flowed between the two hind legs the spinal cord was outside the main pathway.

There have been given three possible explanations for the injury of the spinal cord of rats following electric shocks: (1) The rise in blood pressure following contact with the circuit may produce a break in the artery of the dorsomedian

septum, which gives rise to hemorrhage. (2) The sudden violent flexion of the back at the time the circuit is closed may similarly damage the artery. (3) The current flowing through the cord may disrupt the fiber tracts of the posterior columns where the current density is greatest with secondary capillary hemorrhage. No conclusive case can be made for any one of these theories, but the last, primary damage to the nerve fibers by the current density, seems the most likely.

With regard to the decrease of paralysis and its final failure to appear after repeated shocks, the two possible explanations will be discussed—namely, that all the animals susceptible to paralysis may have been paralyzed by the first few shocks, or that the rats may in some way become immune to the electric current. The first explanation seems perhaps the more likely, but there are certain facts that suggest the development of a kind of immunity to electricity. The first time that the animals were subjected to a circuit at 248 volts, they were all severely injured, and all required artificial respiration. Moreover, they lay quietly for from fifteen minutes to half an hour following the injury and were very slow in becoming active again. They did not eat or drink for twenty-four hours. Following subsequent shocks at the same voltage, the rats breathed normally as soon as the circuit was opened. Moreover, they recovered rapidly and were active at once. The electric shocks, therefore, became progressively less damaging to them.

It became possible to tell immediately after the shock which rats would later become paralyzed. Convulsive movements of the hind legs, tail, and trunk musculature of the posterior portion of the body occurred. The movements of the hind legs were bilateral extensor thrusts. Often the rat would breathe following the shock, and then respirations would cease; after breathing was started again it would be irregular and gasping. The paralyzed rats showed no activity following the shock.

This series of continued shocks differed from all the authors' previous experiments, in that a few rats developed a slight weakness and paralysis of the hind legs after a number of contacts. This paralysis was not severe enough to kill the rats and they were carried along with the rest of the series. The hind legs became hyperextended; the paralysis tended to decrease after several days or weeks.

In considering the paralysis of the hind legs of rats it must be realized that this result of electric shock is not seen in man, although it is said to occur in other experimental mammals. Since it is such a common result of electric injury in rats, it has been found useful as a criterion of the damage produced by the circuit.

At the higher voltages a number of rats died as an immediate result of the shock. Pulmonary hemorrhage and edema were an incident in the death of all these rats, if not the actual cause; when bloody and frothy fluid gushed from the mouth and nose, it was clear that artificial respiration would not initiate breathing. Small hemorrhages, probably dependent upon capillary bleeding from the mucous membrane of the nose, occurred in many rats that recovered quite normally.

Bleeding from the eyes was common after each shock, owing to rupture of capillaries in the conjunctiva; often the hemorrhage was quite profuse. Table 4 shows that it did not occur after contact with circuits at 8 and 13 volts, but when the voltage was raised to 15, it was present in three out of twenty rats, and at 17.5 volts in fourteen out of twenty. Staining of the hair around the eyes was taken as the criterion. The bleeding showed no increase or diminution following successive shocks.

There were other phenomena in connection with the eyes that were observed for the first time in this series. Immediately after the circuit was broken, the pupils were widely dilated; gradually they became constricted again. After contacts with circuits at 250 volts or over, the eyes were often turned upward and outward, but they gradually returned to normal.

Certain of the rats developed signs of vestibular disturbances after one of the electric shocks. Even though they survived and were carried safely through the series, this abnormality in equilibrium persisted until the end of the experiment.

The rats of these series were almost exclusively males and emission was noted in nearly every case at each shock. This is probably due to the strong contraction of the entire body musculature. Table 4 shows the lowest voltage at which emission occurred. It was noticed in one rat out of twenty shocked from a circuit at 8 volts, but in none of those subjected to a 13-volt circuit. With circuits at 15, 17.5, and 23 volts it was found in a small percentage, and with circuits at 30 or more volts it occurred constantly in the majority.

In the previous experiments of the authors with a single electric shock, priapism was observed only in males shocked from a continuous circuit at 1,000 volts. Priapism was an abnormality that appeared in a few of the rats in the present group after a number of shocks, and it was considered a sign of severe irritation and damage to the spinal cord. It was noticed in five of the 111 rats of Table 2. A number of these rats lived and continued in the series to the end.

From the results here reported, it is evident that animals differ widely in their susceptibility to electric shock. This difference depends to some extent upon the age, weight, and sex of the animals but to a much greater extent upon more complex biologic factors. If this difference in susceptibility to electric shock may be assumed to hold for all mammals, it is important to look for some means of selecting those animals that will be injured by contact with an electric circuit. No method of exact correlation has yet been devised but experiments along this line are planned. There is also experimental evidence that rats develop a degree of immunity to repeated electric shocks.

Summary

Rats were subjected to repeated contacts with electric circuits at three-day intervals. After contact with a circuit of 248 volts, a certain proportion of the animals showed a paralysis of the hind legs. The incidence of paralysis decreased rapidly with subsequent shocks and disappeared en-

tirely even though the voltage was raised to 1,000 volts. This suggests either that the rats susceptible to the electric current are injured with the first shocks or that the rats become immune to electricity. In favor of the latter hypothesis is the fact that the respiratory paralysis and the time required for recovery decreased steadily with an increase in the number of shocks. The mechanism of the paralysis is discussed. After a number of shocks certain rats developed disturbances of equilibrium, priapism, and other signs of hyperirritability of the nervous system.

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BOOK REVIEWS

Exercise and its Physiology. By *Adrian Gordon Gould*, Ph.B., M.D., Assistant Medical Adviser and Assistant Professor of Hygiene in Cornell University; and *Joseph A. Dye*, A.B., Ph.D., Assistant Professor of Physiology in Cornell University. Cloth. Pp. xi, 434 with index and illustrations. New York: A. S. Barnes & Co., Inc., 1932.

In no field of physiology has there been within the past few years more rapid growth than in that of the physiology of exercise. Most of the recent work on this subject has not been incorporated into any textbook of physiology and thus a great deal of the new material has not been easily accessible to the lay reader. Although there has been a recent revision of that excellent monograph by F. A. Bainbridge on "The Physiology of Muscular Exercise," such a summary of the more recent work as is embodied in this book was due.

In this book the authors have successfully brought up to date the subject of the physiology of exercise. The material, which includes a digested compilation of facts made available by recent work, is presented in a logical and thoroughly readable manner. The book is well illustrated. Each chapter contains at the end a brief summary and many references. It should be most useful as a text and for reference, not only for teachers and students of physical education but for students of physiology and medicine and for anyone interested in the effects of exercise on the human body. —*Madeleine E. Field.*

INDUSTRIAL HYGIENE FOR ENGINEERS AND MANAGERS. By *Carey P. McCord*, M.D., Medical Director, The Industrial Health Conservancy Laboratories, Cincinnati, Ohio. Assisted by Floyd P. Allen, M.D., The Public Health Federation. Cloth. Pp. x, 336 with index and illustrations. New York and London: Harper & Brothers, 1931.

On the jacket of this book the publishers state that it is "a practical reference manual on all phases of industrial hygiene," intended for the guidance of "plant managers, industrial engineers, industrial doctors and nurses." The materials that make up the book have "for ten years been presented to students in the Engineering College of the University of Cincinnati. While this subject has been given only a minor position in an overfilled program of engineering training, a proper concept of the requirements of human conservation in industry has been obtained by at least a portion of these prospective engineers." It is extraordinarily difficult to convince the average plant manager that industrial health conservancy is a paying investment. Numerous companies in the United States today find themselves pursued by compensation suits, some of which are unjust, and many of which could have been avoided by routine preventive work.

This book is precisely what the publishers claim—a reference manual in industrial hygiene. It is well indexed, the topics for the twenty chapters are well and logically selected, and the reader is freed from having to choose between controversial opinions and a mass of detailed references. The tabulated data of general symptoms to be expected from exposures to various chemicals, minerals, gases, and the like are given in a practical but brief and concise form.

There are chapters devoted to emergency aid, bandaging, infection and disinfection, occupational diseases, sanitation, accident prevention, physical examinations, medical and dental care, compensation, and sources of technical information.

In the reviewer's opinion this book will serve a useful purpose as a manual or guide for plant managers. The fact that an eminent publishing house sees fit to bring out the book at this time is in itself a good omen. That the book contributes to the purely scientific aspects of industrial hygiene is doubtful.—*Philip Drinker.*

J. I. H.
May, 1932